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Obinutuzumab versus Rituximab in young patients with advanced DLBCL, a PET-guided and randomized phase 3 study by LYSA

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Abstract:

Rituximab plus polychemotherapy is standard of care in diffuse large B-cell lymphoma (DLBCL). GAINED trial compares obinutuzumab to rituximab. GAINED (NCT01659099) is an open-label, randomized phase 3 trial. Transplant-eligible patients (18-60yrs) with untreated aged-adjusted international prognostic index (aaIPI) ≥ 1 DLBCL were randomized (1:1) between obinutuzumab or rituximab. Patients were stratified by aaIPI (1; 2-3) and chemotherapy regimen (ACVBP; 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 immuno-chemotherapy consolidation. Responders only after cycle 4 (PET2+/4-) received high-dose methotrexate plus transplantation. The primary objective was an 8% improvement (HR=0.73; 80% power; alpha risk 2.5%; one-sided) in 2-year event-free survival (EFS) in the obinutuzumab arm. Events included death, progression, PET 2 or 4 positivity, modification of planned treatment. From September 20, 2012, 670 patients were enrolled (obinutuzumab n=336; rituximab n=334). 383 (57.2%) were aaIPI 2-3, 339 (50.6%) received CHOP and 324 (48.4%) received ACVBP. Median follow-up was 38.7 months. The 2-year EFS were similar in obinutuzumab and rituximab groups (59.8% vs 56.6%; p=0.123; HR=0.88). The 2-year PFS in the whole cohort was 83.1% (95%CI 80-85.8). PET2-/4- and PET2+/4- had similar 2-year PFS and OS (89.9% vs 83.9%) and 94.8% vs 92.8%). The 2-year PFS and OS for PET4+ patients were 62% and 83.1%. Grade 3-5 infections were more frequent in the obinutuzumab arm (21% vs 12%). Obinutuzumab is not superior to rituximab in untreated aaIPI ≥ 1 DLBCL transplant-eligible patients.

Conflict of interest: COI declared - see note

COI notes: SLG reports grants, personal fees or non-financial support from Roche Genentech, during the conduct of the study; reports personal fees from Celgene, reports grants and personal fees from Janssen-Cilag; GILEAD/kite, Servier outside the submitted work; HG reports grants, personal fees or non-financial support from Gilead Sciences, Janssen, Celgene, Roche, Takeda; LO, Advisory board: Roche, Takeda; honoraria: Celgene, Janssen, Roche; FM has received honoraria from Bristol-Myers Squibb and Janssen and served as a consultant or advisor to Celgene, Bayer, Abbvie, Verastem, Gilead, Servier, Roche/Genentech, and Epizyme; HT, Consulting and advisory board: Roche, Janssen-Cilag, Karyopharm, Astra-Zeneca, Lectures: Roche, Bristol-Myers-Squibb, Servier ; VR, Infinity Pharmaceuticals, Bristol-Myers Squibb, PharmaMar, Gilead Sciences, AZD, Epizyme, Incyte, MSD, Servier, Roche, arGEN-X BVBA; CT Honoraria: Amgen , Celgene, Jazz Pharma, Kyte/ Gilead, Novartis, Servier, Roche, Janssen; Research funding: Roche, Celgene, Aspira; CH reports Takeda, AbbVie; Honoraria and non-financial support: Roche, Janssen-Cilag, AbbVie, Takeda ; GD, Board : Roche, taked ; Travel : Roche AbbVie Pfizer, Grants : takeda, roche; LF, Honoraria : Roche, Janssen, Gilead, Servier, Takeda ; Travel grant : Rochen Janssen, Abbvie, Takeda ; Board : Roche, Servier, Takeda; PF Roche Genentech, celgene, Abbvie, Janssen and gilead; OH, Celgene research grant, Alexion research grant, Ab science co founder research grant consulting, Inatherys co founder research gérants; GC has received honoraria from Janssen, Sanofi, Abbvie, Gilead, Roche, Celgene and served as a consultant or Celgene, Roche/Genentech; CB is board

member for Roche; CBM, consulting BMS and Gilead; TJM, consulting Merck and Novartis; ROC reports grants, personal fees and non-financial support from Roche Genentech, during the conduct of the study; reports personal fees from MSD, BMS, Abbvie, Amgen, Celgene, reports grants and personal fees from Takeda, GILEAD/kite, outside the submitted work; All other authors declare no competing interests (HM, KB, LC, JPJ, FKB, JB, ABR, EI, TL, RG MA, RB)

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Author contributions and disclosures: SLG and ROC contributed equally to this work: they designed the trial (in collaboration with GS, JPJ, CH, EI, TL), conducted the study, analyzed the results, enrolled and treated patients, wrote the first draft of the manuscript GS, LO, FM, HT, VR, TL, CT, HM, RG, KB, CH, GD, LF, RB, PF, OH, GC, CB enrolled and treated patients. LC and JPJ performed statistical analysis TM and JB performed pathology review EI, FKB, CBM, ABR performed PET review All authors approved the final version of the manuscript and are accountable for all aspects of the work.

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Agreement to Share Publication-Related Data and Data Sharing Statement: Request for access to the study data can be asked by email to the corresponding authors. Request for access to the study data can be asked by email to the corresponding author. This includes deidentified individual participant data, informed consent form, data dictionary defining each field in the set. These data will be available after final publication of all endpoints including secondary endpoints, as listed in the protocol. All requests need to be approved by the corresponding author and aim of the demand should be described and needs to be related to a scientific work. Please notice that the following data are already available in the appendix: study protocol, statistical analysis plan.

Clinical trial registration information (if any): NCT01659099

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Key points

Obinutuzumab does not provide any significant additional tumor control in newly diagnosed transplant-eligible DLBCL compared to rituximab

Interim PET staging enables accurate monitoring and could be considered for use in routine practice of patients with advanced DLBCL

ABSTRACT

Rituximab plus polychemotherapy is standard of care in diffuse large B-cell lymphoma (DLBCL). GAINED trial compares obinutuzumab to rituximab. GAINED (NCT01659099) is an open-label, randomized phase 3 trial. Transplant-eligible patients (18-60yrs) with untreated aged-adjusted international prognostic index (aaIPI) ≥ 1 DLBCL were randomized (1:1) between obinutuzumab or rituximab. Patients were stratified by aaIPI (1; 2-3) and chemotherapy regimen (ACVBP; 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 immuno-chemotherapy consolidation. Responders only after cycle 4 (PET2+/4-) received high-dose methotrexate plus transplantation. The primary objective was an 8% improvement (HR=0.73; 80% power; alpha risk 2.5%; one-sided) in 2-year event-free survival (EFS) in the obinutuzumab arm. Events included death, progression, PET 2 or 4 positivity, modification of planned treatment. From September 20, 2012, 670 patients were enrolled (obinutuzumab n=336; rituximab n=334). 383 (57.2%) were aaIPI 2-3, 339 (50.6%) received CHOP and 324 (48.4%) received ACVBP. Median follow-up was 38.7 months. The 2-year EFS were similar in obinutuzumab and rituximab groups (59.8% vs 56.6%; p=0.123; HR=0.88). The 2-year PFS in the whole cohort was 83.1% (95%CI 80–85.8). PET2-/4- and PET2+/4- had similar 2-year PFS and OS (89.9% vs 83.9%) and 94.8% vs 92.8%). The 2-year PFS and OS for PET4+ patients were 62% and 83.1%. Grade 3-5 infections were more frequent in the obinutuzumab arm (21% vs 12%). Obinutuzumab is not superior to rituximab in untreated aaIPI ≥ 1 DLBCL transplant-eligible patients.

INTRODUCTION

Polychemotherapy regimen (such as CHOP or ACVBP) plus Rituximab is a standard of care in diffuse large B-cell lymphoma (DLBCL)¹⁻⁵. Obinutuzumab is a glycoengineered type II anti-CD20 monoclonal antibody designed to enhance the antibody-dependent cell mediated cytotoxicity as compared to Rituximab. Indeed, the addition of Obinutuzumab to induction chemotherapy may provide a better disease control compared to rituximab plus chemotherapy in previously untreated DLBCL patients presenting with risk factors at diagnosis (aged-adjusted international prognostic index (aaPI) ≥ 1).

Selected young patients with adverse prognostic factors plus insufficient response after induction treatment might benefit from a consolidation treatment⁶⁻⁸ such as autologous stem cell transplantation (ASCT). Interim-PET analysis using a semiquantitative approach (so-called Δ SUVmax) might help to earlier identify patients for whom ASCT could improve disease control⁹⁻¹².

The aim of the GAINED trial is to compare obinutuzumab to rituximab when combined with an intensified chemotherapy regimen delivered every 14 days (ACVBP-14 or CHOP-14) followed by a PET-driven consolidation in untreated patients <60yrs with advanced DLBCL.

METHODS

Study design and participants

This open-label (NCT01659099), multicenter randomized phase 3 study was designed by the Lymphoma Study Association (LYSA) and conducted in 99 centers (Belgium and France). Eligible patients were 18 to 60 years old with newly diagnosed untreated histologically proven CD20+ DLBCL (2008 WHO classification), aaPI ≥ 1 , at least one hypermetabolic lesion at baseline PET, 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. The study was approved by the French and Belgian Health authorities, the Ouest VI (Brest, France) ethics committee and by the institutional review boards in Belgium. It was performed in accordance with the Declaration of Helsinki and Guidelines for Good Clinical Practice, patients provided written informed consent.

Procedures

Patients were enrolled by center with the LYSARC e-Rando system and randomly assigned 1:1 to receive either rituximab or obinutuzumab. Randomization was done centrally with the permuted block method and stratified according to chemotherapy (CHOP vs ACVBP) and age-adapted international prognosis index (aaPI: 1 vs 2-3). The randomization list was generated by LYSARC. Patients and investigators were not masked as to treatment allocation.

Study design is shown in figure 1. Treatment was divided in two phases, induction and consolidation. Induction consisted in 4 courses of CHOP or ACVBP delivered every 14 days. At its opening, each center was asked to choose either CHOP or ACVBP, and all patients included in the center were treated with the same chemotherapy regimen. All chemotherapy regimens are detailed in the full version of the protocol (supplemental data). In addition to CHOP or ACVBP, patients received obinutuzumab (O-CHOP or O-ACVBP) or rituximab (R-CHOP or R-ACVBP) according to randomization. Rituximab (375mg/m²) and obinutuzumab (1g flat dose) were infused at d1 of each cycle, except for cycle 1 where one infusion of obinutuzumab (1g flat dose) was given at d8. Prophylaxis for CNS involvement included 15mg of methotrexate IT at day 1 of the first four cycles.

Responses during induction were assessed by PET. 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). Patients were scanned on the same camera for all PET scans. Whole-body acquisition from groin to head was started within 60±10 min of injection of 5 MBq/kg 18F-FDG. Interpretations of PET2 and PET4 were based on the Δ SUVmax method. PET images were sent through a web platform and masked for independent central review by four expert reviewers (EI, ABR, FB, CBM). Δ SUVmax was calculated as: Δ SUVmax = 100[(SUVmaxPET0 – SUVmaxPETX)/SUVmaxPET 0] as previously described⁹⁻¹¹. For PET2, the Δ SUVmax cut-off was 66% (PET2 considered as negative if Δ SUVmax>66% and positive if \leq 66%)⁹. For PET4, the Δ SUVmax cut-off was 70% (PET4 considered as negative if Δ SUVmax>70% and positive if \leq 70%). 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 Δ SUVmax>66% for PET2 or Δ SUVmax>70% for PET4. This was recommended by the 2011 Menton workshop¹³. The centrally reviewed PET results were then sent back to the investigators, together with the per-protocol recommended consolidation treatment allocation for all patients.

The consolidation phase was adapted to PET2 and 4 results. Patients in response after cycle 2 (Δ SUVmax < 66%) and 4 (Δ SUVmax <70%) (PET2-/4-) received consolidation therapy. For patients treated with CHOP, this consisted of 4 courses of O- or R- CHOP. For patients treated by O- or R- ACVBP this consisted of 2 cycles of high-dose methotrexate (3g/m²) every 14 days followed by four cycles of ifosfamide (1.5g/m² at D1) plus etoposide (300mg/m² at D1) every 14 days, and two cycles of sub-cutaneous cytarabine (100mg/m² for 4 days) delivered every 14 days for. Patients received obinutuzumab or rituximab according to initial randomization. Patients in response after cycle 4 but not after cycle 2 (PET2+/4) received two courses of high-dose methotrexate (3g/m²) every 14 days followed by autologous stem cell transplantation (ASCT). The conditioning regimen for ASCT was BEAM (details in supplemental data). Collection of peripheral blood stem cell progenitors was organized after induction cycle 3 or 4 for PET2+ patients. The target dose of collected CD34+ cells was 3x10⁶ cells/kg. Patients who did not reach response after cycle 4 and regardless response after cycle 2 (PET4+) were classified as non-responders and salvage therapy was considered at the discretion of the local investigator.

In addition to PET, the following assessments were also mandatory: CT at diagnosis and after four cycles of chemotherapy, at the end of treatment, and every 6 months until the end of follow-up; bone-marrow (BM) biopsy at baseline to confirm complete remission in patients with positive BM at baseline and haematological

laboratory assessments at inclusion and before each cycle of chemotherapy. All diagnoses were performed by local pathologists and centrally reviewed by two LYSA-pathology experts. The Cell of origin (COO) of DLBCL was analyzed by Nanostring technology and according to the Hans algorithm.

Trial treatments were stopped in the following cases: lymphoma progression, toxic effects from study treatment, concomitant illness or protocol violations that precluded continuation, start of a new treatment for lymphoma, consent withdrawal, or refusal to continue treatment

Adverse events were assessed after each cycle of chemotherapy and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0, and treatment-related toxicities were reported by study group.

Outcomes

The primary endpoint was the 2-year event-free survival (EFS). EFS was defined as the time from randomization to PET positivity (according to Δ SUVmax criteria after cycle 2 or 4 based on central PET review), progression or relapse (according to Cheson 2007 criteria), modification of planned treatment non-related to progression (including radiotherapy), death of any cause. For patients who were not PET positive after cycle 2 or 4, or who had not progressed, relapsed, received a new anti-lymphoma treatment non-related to progression and were alive at the time of analysis, EFS was censored at the date of last disease assessment. The key secondary endpoints were safety, early metabolic response according to PET after cycles 2 and 4, overall response rate and best overall response rate after 4 cycles and end of treatment according to Cheson 2007 and 1999 criteria, duration of response (DOR), progression-free survival (PFS) and overall survival (OS).

Statistical analysis

We assessed the efficacy of obinutuzumab compared to rituximab in terms of EFS. We hypothesized superiority of the obinutuzumab arm as an 8% or higher improvement of 2-year EFS compared to the rituximab arm. This would correspond to a 2-year EFS greater than 73% in the obinutuzumab arm. Superiority would be established if the upper limit of the hazard ratio was lower than 0.73 with an alpha of 2.5% (one-sided test) and a power of 80%. We used an exponential model to calculate sample size. Hypothesis calculation was based on an estimate of 65% 2-year EFS in the rituximab treatment group. We planned to enroll 670 patients, including an estimated 10% drop out, to observe a total of 345 EFS events. Two interim analyses of the primary endpoint were planned (according to the Lan-DeMets sequential designed to test futility and superiority) after 33% and 66% of the scheduled events needed for the final analysis had been recorded. The first interim analysis was performed in 2015 (data cutoff date April 14, 2014): the unilateral logrank p value ($p=0.0573$) for stratified EFS was inferior to the preplanned futility bound ($p=0.5856$) and superior to the preplanned superiority bound ($p=0.0001$). This led the data and safety monitoring committee to recommend continuation of the study. The second interim analysis was performed in 2017 (data cutoff date August 1, 2016): the unilateral logrank p value ($p=0.1321$) for stratified EFS was superior to the preplanned futility bound ($p=0.069$) leading the data and safety monitoring committee to recommend stopping the study for futility. As all the patients were enrolled at the time of the second interim analysis with only 25.2 months of median follow-up, the data and safety monitoring committee recommended monitoring patients for at least 1 additional year before presenting the final results of the trial.

The data cutoff for the present analyses was December 1, 2017. The EFS, progression-free survival (PFS), OS and duration of response (DOR) analyses were done with an intention-to-treat (ITT) method, thus including all patients randomly assigned to a treatment group. Prespecified sensitivity analyses such as unstratified analyses, analysis based on efficacy set (ES) and analysis based on per protocol set (PP), were performed for the primary endpoint. The efficacy set (ES) included all patients randomized who received at least one dose of monoclonal antibody and had PET2 and PET4 (unless there was previous disease progression). The per protocol set (PP) excluded patients with major protocol deviations. Safety was assessed in patients who received at least one dose of study treatment (obinutuzumab or rituximab).

Survival estimates with 95% CIs were calculated with the Kaplan-Meier method. The survival distributions were compared with the log-rank test, and Cox proportional hazard regression models were used to estimate HRs and associated 95% CIs.

To compare the relative effect of the full PET-driven strategy on progression-free (PFS) and overall survival (OS) according to baseline characteristics found to influence outcomes in univariate analysis, a Cox proportional hazard regression model was fitted, including PET profile and aaIPI as explanatory variables. Response and PET2 and PET4 results were expressed with 95% exact Clopper Pearson CI limits and compared with the χ^2 test. Differences between groups were significant if p values were less than 0.025 (one-sided) for EFS and less than 0.05 (two-sided) for PFS and OS.

Funding source

Roche pharma provided obinutuzumab and funded the trial. The funder had no role in trial design, data collection, data analysis, data interpretation, or writing of the report. Corresponding authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. LYSARC is the sponsor

RESULTS

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 obinutuzumab (n=336). Patients' characteristics at baseline (table 1) were well balanced across the two treatment groups (and according to chemotherapy, see appendix), except for gender (p=0.016). The median age at baseline was 48 years (18–61). Median time from diagnosis to treatment was 20 days (2-149). Six hundred and forty-six (96.4%) out of 670 patients underwent a centrally assessed pathology biopsy, among whom 580 (86.6%) had a confirmed CD20+ DLBCL.

Among the 670 enrolled patients, 339 patients received at least one cycle of CHOP (with obinutuzumab in 169 cases and rituximab in 170 cases) and 324 received at least one cycle of ACVBP (with obinutuzumab in 163 cases and rituximab in 161 cases) (table 1). Three hundred and twelve patients out of 336 (93%) and out of 334 (93%) completed induction treatment in the obinutuzumab and rituximab arms, respectively (figure 2). Reasons for treatment discontinuation during induction were mainly treatment-related toxicity (n=16; 2.4%). After completion of induction, main reasons for treatment discontinuation in PET4 negative patients were treatment-related toxicity in 31 patients (6.4%), major protocol violation in 10 patients (2.0%) and patient decision in 14 cases (2.9%).

PET2 and 4 were performed in 302 (90%) and 297 (88%) in the obinutuzumab arm and 302 (90%) and 289 (86.5%) patients in the rituximab arm. PET2 and PET4 positivity rates were slightly higher in the rituximab arm compared to the obinutuzumab arm but did not reach statistical significance (table 2). As shown in figure 2, 401 (69%) were PET2-/4- of whom 398 (99.3%) received the planned immunochemotherapy. Eighty seven (15%) patients were PET2+/PET4- of whom 74 (85%) received the planned consolidation therapy followed by ASCT. Ninety three patients (16%) had positive PET4 of whom 91 (97.8%) received salvage therapy. In all, 227 patients (68%) completed the planned treatment in the obinutuzumab 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 (figure 2)).

The median follow-up after randomization was 38.7 months (95%CI 36.9-40.0). For the primary efficacy analysis (ITT set), 147 (43.8%) in the obinutuzumab arm and 155 (46.4%) in the rituximab arm had an event. Most frequent events were PET 2 or 4 positivity (85 patients (25%) in the obinutuzumab arm and 107 patients (32%) in the rituximab arm) (see appendix). The 2-year EFS estimates were 59.8% (95%CI 54.3-64.8) in the obinutuzumab arm and 56.6% (95%CI 51.1-61.8) in the rituximab arm (stratified logrank: p=0.123; unstratified Logrank: p=0.127; HR=0.88, 95%CI 0.7-1.1) (figure 3a) and did not differ according to both chemotherapy and aaPI in both arms (table 3). The efficacy of obinutuzumab and rituximab in terms of EFS was consistent across prespecified subgroups except for patients of 50 years old or younger (HR=0.71, 95%CI 0.5-0.9), and for those with at least 40% of tumor cells expressing MYC (HR=0.55, 95% CI 0.4-0.8) (figure 4a). EFS in the efficacy set (n=617) did not differ significantly between the two arms (stratified logrank: p=0.077, unstratified logrank: p=0.074; HR=0.84, 95%CI 0.7-1.1; figure 3b). In the PP set, results were similar (stratified logrank: p=0.055; unstratified logrank: p=0.056; HR=0.83, 95%CI 0.6-1.0; figure 3c).

Response rates after 4 cycles of induction and at the end of treatment (according to Cheson 1999 and 2007 (see appendix)) were similar in both arms. Duration of response (Cheson 2007 criteria) did not differ significantly between the two arms (2 and 4-year DOR: 87.4% (95%CI 83.1-90.7) and 82.8% (95%CI 77.4-87.0) vs 86.8% (95%CI 82.3-90.2) and 83.4% (95%CI 78.2-87.4), HR=0.98 (95%CI 0.7-1.5), p=0.94) (see appendix). PFS did also not differ significantly between the two arms (p=0.87; HR=1.03, 95%CI 0.7-1.4). The 2 and 4-year PFS estimates in the ITT population were respectively 83.2% (95%CI: 78.7-86.8) and 77.5% (95% CI: 72.2-81.9) in the obinutuzumab arm and 83% (95%CI 78.5-86.7) and 78.8% (95%CI 73.8-83) in the rituximab arm (figure 5). Results were similar in the ES (p=0.92) and PP sets (p=0.96). The efficacy of obinutuzumab and rituximab in terms of PFS was similar across prespecified subgroups (figure 4b). OS was similar between both arms (p=0.85; HR=0.96, 95%CI 0.6-1.5). The 2 and 4-year OS were respectively 90.7% (95%CI 87.0-93.4) and 88.2% (95%CI 83.9-91.4) in the obinutuzumab arm vs 91.8% (95%CI 88.1-94.3) and 86% (95%CI 80.8-89.8) in the rituximab arm (figure 5). 70 out of 663 patients (safety set) (10.6%) died of whom 34 (10.2%) were in the obinutuzumab arm and 36 (10.9%) were in the rituximab arm. Main causes of death were lymphoma in 45 patients (6.8%) (19 in the obinutuzumab and 26 in the rituximab arms) and toxicity of the study treatment in 9 patients.

A univariate analysis showed that Ann Arbor Stage III-IV, ECOG status >1, aaIPI>1, tumor bulk ≥ 10 cm, Bcl2 expression in $\geq 70\%$ of tumor cells, were associated with lower PFS (table 4). On the other hand, LDH level, COO according to the Hans algorithm or gene expression profile, MYC expression, and double expression of BCL2 and MYC had no effect on PFS. Ann Arbor Stage III-IV, ECOG status >1, aaIPI>1 were also associated with a worse OS. By contrast, LDH level, tumor bulk, COO that had no significant effect. A positive PET2 was not associated to an inferior outcome when PET4 was negative. PET2-/PET4- patients assigned to immunochemotherapy and PET2+/PET4- patients allocated to ASCT had similar PFS (2 and 4-year PFS: 89.9% (95%CI 86.5-92.5) and 83% (95%CI 78.5-86.7) vs 83.9% (95%CI 74.3-90.1) and 83.9% (95%CI 74.3-90.1)) and OS (2 and 4-year OS: 94.8% (95%CI 92.1-96.6) and 90.3% (95%CI 86.2-93.2) vs 92.8% (95%CI 84.7-96.7) and 90.2% (95%CI 81.4-95)). Conversely, PET4 positivity was associated with an increased risk of relapse, progression or death, regardless of the treatment group (2 and 4-year PFS: 62% (95%CI 51.3-71) and 60.9% (95%CI 50.1-70), HR=3.44, 95%CI 2.3-5.1; p<0.001; 2 and 4-year OS: 83.1% (95%CI 73-89.7) and 81.5% (95%CI 71.1-88.5), HR=2.49, 95%CI 1.4-4.5; p=0.005) (figure 6). In a multivariable analysis PET4 positivity was the only parameter that remained statistically significant for both PFS and OS (p<0.001) while patients with IPI 2-3 (p=0.001) and percentage of Bcl-2 positive cells $\geq 70\%$ (p=0.047) presented a worse OS but not PFS. Ann Arbor stage III-IV (p<0.001) and bulky disease (p=0.039) were statistically significant for PFS but not for OS (table 4).

During induction phase, the most common grade 3-4 adverse events in the safety set were hematological as nearly half of the patients experienced neutropenia in both arms. Grade 3-5 infections were more frequent in the obinutuzumab arm (21%) compared to the Rituximab arm (12%). Other AEs were standard for intensive chemotherapy (See appendix table 7). The cumulative incidence of second primary malignancies was 4.1% in 27 patients and similar between the two groups (15 (4.5%) in 332 patients of the obinutuzumab arm and 12 (3.6%) in 331 patients of the Rituximab arm) while more acute leukemia or myelodysplasia syndrome were observed in the obinutuzumab arm (6 vs 2 cases) (see appendix).

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DISCUSSION

The GAINED trial demonstrates that obinutuzumab does not provide better EFS than rituximab in combination with chemotherapy delivered every 14 days for treatment-naïve young patients with IPI \geq 1 DLBCL. PFS and OS are similar in both arms. Analysis of subgroups does not show a subset of patients who may benefit from obinutuzumab rather than rituximab.

The GALLIUM¹⁴ study demonstrated that, in newly diagnosed follicular lymphoma patients, obinutuzumab plus chemotherapy followed by an obinutuzumab maintenance significantly improves PFS compared to the same treatment with rituximab. In contrast, the GOYA trial¹⁵ fails to show superiority of obinutuzumab 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 obinutuzumab 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 obinutuzumab infusions associated to CHOP21 while GAINED compares rituximab vs obinutuzumab 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 obinutuzumab 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 \geq 1^{6,8,16,17}. 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^{6,12}. A post Hoc analysis of the LNH07-3B study shows that Δ SUVmax improves the prognosis value of interim PET after cycles 2 and 4 compared to visual analysis^{6,11}. In the present study, Δ SUVmax is used prospectively in order to interpret interim PET and to discriminate patients with different outcomes. The PETAL study which uses the Δ SUVmax method with the same 66% cut-off after 2 cycles of immunochemotherapy^{9,11,18}, demonstrates that DLBCL patients have significantly better outcomes when Δ SUVMax>66%¹⁷. It is interesting to compare the efficacy of the consolidation strategy applied to PET2+/PET4- 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 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 versus a non-transplant therapy. 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 Δ SUVmax. 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 regimen are used in daily practice, such as DA-EPOCH or ACVBP. ACVBP demonstrated superiority over CHOP in aaIPI=1 patients⁵. 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-CHOP²⁰⁻²². 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 volume²³⁻²⁵ and interim-PET results added to longitudinal analysis of ctDNA^{26,27} could provide an interesting multi-parameters approach capable of refining the prediction of early response to treatment.

In conclusion, obinutuzumab 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 Δ SUVmax criteria enables early identification of patients with high risk of relapse for whom innovative therapeutic solutions are needed.

Authorships

SLG and ROC contributed equally to this work: they designed the trial (in collaboration with GS, JPJ, CH, EI, TL), conducted the study, analyzed the results, enrolled and treated patients, wrote the first draft of the manuscript

GS, LO, FM, HT, VR, TL, CT, HM, RG, KB, CH, GD, LF, RB, PF, DS, GC, CB enrolled and treated patients.

LC and JPJ performed statistical analysis

TM and JB performed pathology review

EI, FKB, CBM, ABR performed PET review

All authors approved the final version of the manuscript and are accountable for all aspects of the work.

Declaration of interests

SLG reports grants, personal fees or non-financial support from Roche Genentech, during the conduct of the study; reports personal fees from Celgene, reports grants and personal fees from Janssen-Cilag; GILEAD/kite, Servier outside the submitted work; **HG** reports grants, personal fees or non-financial support from Gilead Sciences, Janssen, Celgene, Roche, Takeda; **LO**, Advisory board: Roche, Takeda; honoraria: Celgene, Janssen, Roche; **FM** has received honoraria from Bristol-Myers Squibb and Janssen and served as a consultant or advisor to Celgene, Bayer, Abbvie, Verastem, Gilead, Servier, Roche/Genentech, and Epizyme; **HT**, Consulting and advisory board: Roche, Janssen-Cilag, Karyopharm, Astra-Zeneca, Lectures: Roche, Bristol-Myers-Squibb, Servier ; **VR**, Infinity Pharmaceuticals, Bristol-Myers Squibb, PharmaMar, Gilead Sciences, AZD, Epizyme, Incyte, MSD, Servier, Roche, arGEN-X BVBA; **CT** Honoraria: Amgen , Celgene, Jazz Pharma, Kyte/ Gilead, Novartis, Servier, Roche, Janssen; Research funding: Roche, Celgene, Aspira; **CH** reports Takeda, AbbVie; Honoraria and non-financial support: Roche, Janssen-Cilag, AbbVie, Takeda ; **GD**, Board : Roche, Takeda ; Travel : Roche AbbVie Pfizer, Grants : Takeda, Roche; **LF**, Honoraria : Roche, Janssen, Gilead, Servier, Takeda ; Travel grant : Roche Janssen, Abbvie, Takeda ; Board : Roche, Servier, Takeda; **PF** Roche Genentech, Celgene, Abbvie, Janssen and Gilead;; **GC** has received honoraria from Janssen, Sanofi, Abbvie, Gilead, Roche, Celgene and served as a consultant or Celgene, Roche/Genentech; **CB** is board member for Roche; **CBM**, consulting BMS and Gilead; **TJM**, consulting Merck and Novartis; **ROC** reports grants, personal fees and non-financial support from Roche Genentech, during the conduct of the study; reports personal fees from MSD, BMS, Abbvie, Amgen, Celgene, reports grants and personal fees from Takeda, GILEAD/kite, outside the submitted work; All other authors declare no competing interests (**HM, KB, LC, JPJ, FKB, JB, ABR, EI, TL, RG MA, RB, DS**)

Data sharing

Request for access to the study data can be asked by email to the corresponding authors. Request for access to the study data can be asked by email to the corresponding author. This includes deidentified individual participant data, informed consent form, data dictionary defining each field in the set. These data will be available after final publication of all endpoints including secondary endpoints, as listed in the protocol. All requests need to be approved by the corresponding author and aim of the demand should be described and needs to be related to a scientific work. Please notice that the following data are already available in the appendix: study protocol, statistical analysis plan.

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FIGURES AND TABLES LEGENDS

Table 1 : Patients' characteristics at baseline. ITT, intention-to-treat ; ECOG , Eastern Cooperative Oncology Group scale ; LDH, lactate deshydrogenase ; aaIPI, age-ajusted International prognostic index ; DLBCL, diffuse large B-cell lymphoma ; COO, cell of origin; GCB, germnial-center B-cell ; ABC, activated B-cell ; DE, double expressor ; CHOP, cyclophosphamide (750mg/m² at D1), doxorubicine (50mg/m² at D1), vincristine (1.4mg/m², max 2mg, at D1) and prednisone (40mg/m² D1-D5) ; ACVBP included doxorubicine (75mg/m² at D1), prednisone (60mg/m² D1-D5), cyclophosphamide (1200mg/m² at D1), vindesine (2mg/m² at D1 and 5) and bleomycine (10mg at D1 and 5).

Table 2: interim-PET results according to the central review in the ITT population. CHOP, cyclophosphamide (750mg/m² at D1), doxorubicine (50mg/m² at D1), vincristine (1.4mg/m², max 2mg, at D1) and prednisone (40mg/m² D1-D5) ; ACVBP included doxorubicine (75mg/m² at D1), prednisone (60mg/m² D1-D5), cyclophosphamide (1200mg/m² at D1), vindesine (2mg/m² at D1 and 5) and bleomycine (10mg at D1 and 5).

Table 3: 2y-EFS according to treatment arm in the ITT population. EFS, event-free survival; ITT , intention-to-treat; CHOP, cyclophosphamide (750mg/m² at D1), doxorubicine (50mg/m² at D1), vincristine (1.4mg/m², max 2mg, at D1) and prednisone (40mg/m² D1-D5) ; ACVBP included doxorubicine (75mg/m² at D1), prednisone (60mg/m² D1-D5), cyclophosphamide (1200mg/m² at D1), vindesine (2mg/m² at D1 and 5) and bleomycine (10mg at D1 and 5).

Table 4: Factors influencing patient's outcome. aaIPI, age-ajusted International prognostic index ; ECOG , Eastern Cooperative Oncology Group scale ; LDH, lactate deshydrogenase ; CHOP, cyclophosphamide (750mg/m² at D1), doxorubicine (50mg/m² at D1), vincristine (1.4mg/m², max 2mg, at D1) and prednisone (40mg/m² D1-D5) ; ACVBP included doxorubicine (75mg/m² at D1), prednisone (60mg/m² D1-D5), cyclophosphamide (1200mg/m² at D1), vindesine (2mg/m² at D1 and 5) and bleomycine (10mg at D1 and 5) ; HR, hazard ratio

Figure 1: Study design. DLBCL, diffuse large B-cell lymphoma, C, cycle ; aaIPI, age-ajusted International prognostic index ; MTX, methotrexate ; CHOP, cyclophosphamide (750mg/m² at D1), doxorubicine (50mg/m² at D1), vincristine (1.4mg/m², max 2mg, at D1) and prednisone (40mg/m² D1-D5) ; ACVBP included doxorubicine (75mg/m² at D1), prednisone (60mg/m² D1-D5), cyclophosphamide (1200mg/m² at D1), vindesine (2mg/m² at D1 and 5) and bleomycine (10mg at D1 and 5) ; ASCT autologous stem-cell transplantation ; BEAM, carmustine 300mg/m² at D-6; etoposide 200mg/m² from D-6 to -3; cytarabine 200mg/m²/12H from D-6 to -3; melphalan 140mg/m² at D-2

Figure 2: Flow chart

Figure 3: EFS in ITT (a), ES (b), and PP (c) populations. EFS, event-free-survival; ITT, intention-to-treat; ES, efficacy set; PP, per protocol

Figure 4: Unstratified Hazard ratio for EFS (panel A) and PFS (panel B) in predefined subsets of patients. EFS, event-free survival; PFS, progression-free survival; ECOG , Eastern Cooperative Oncology Group scale ; LDH, lactate deshydrogenase ; aaIPI, age-ajusted International prognostic index ; DLBCL, diffuse large B-cell lymphoma ; GCB, germnial-center B-cell ; ABC, activated B-cell ; DE, double expressor ; CHOP, cyclophosphamide (750mg/m² at D1), doxorubicine (50mg/m² at D1), vincristine (1.4mg/m², max 2mg, at D1) and prednisone (40mg/m² D1-D5) ; ACVBP included doxorubicine (75mg/m² at D1), prednisone (60mg/m² D1-D5), cyclophosphamide (1200mg/m² at D1), vindesine (2mg/m² at D1 and 5) and bleomycine (10mg at D1 and 5).

Figure 5: Unstratified PFS (A) and OS (B) according to randomization arms and PFS according to PET2 PET4 responses in the whole cohort (C) and OS according to iPET response (D). PFS, progression-free survival; OS, overall survival

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Table 1 : Patients' characteristics at baseline

Characteristics	ITT (n=670)		Efficacy set (n=617)		Per Protocol set (n=594)	
	Obinutuzumab (n = 336)	Rituximab (n = 334)	Obinutuzumab (n = 311)	Rituximab (n = 306)	Obinutuzumab (n = 296)	Rituximab (n = 298)
Median age (range), years	49 (19-60)	48 (18-61)	49 (19-60)	47 (18-60)	49 (19-60)	47 (18-60)
Sex, male	203 (60.4%)	170 (50.9%)	189 (60.8%)	153 (50.0%)	180 (60.8%)	152 (51.0%)
ECOG						
0-1	286 (85.1%)	289 (86.8%)	266 (85.5%)	264 (86.3%)	252 (85.1%)	255 (85.6%)
>1	50 (14.9%)	44 (13.2%)	45 (14.5%)	41 (13.4%)	44 (14.9%)	42 (14.1%)
Missing	0	1	1	1	0	1
Ann Arbor stage						
I-II	55 (16.4%)	63 (18.9%)	52 (16.7%)	62 (20.3%)	51 (17.2%)	60 (20.1%)
III-IV	281 (83.6%)	271 (81.1%)	259 (83.3%)	244 (79.7%)	245 (82.8%)	238 (79.9%)
LDH elevated, yes	239 (71.1%)	248 (74.3%)	218 (70.1%)	230 (75.2%)	212 (71.6%)	225 (75.5%)
aalPI						
0	1 (0.3%)	1 (0.3%)	1 (0.3%)	1 (0.3%)	0(0%)	0 (0%)
1	142 (42.5%)	138 (41.7%)	135 (43.4%)	126 (41.2%)	128 (43.2%)	123 (41.3%)
2	149 (44.6%)	156 (47.1%)	136 (43.7%)	143 (46.7%)	129 (43.6%)	138 (46.3%)
3	42 (12.6%)	36 (10.9%)	37 (11.9%)	33 (10.8%)	37 (12.5%)	34 (11.4%)
Extranodal involvement (yes)	273 (81.3%)	271 (81.1%)	255 (82.0%)	238 (77.8%)	243 (82.1%)	233 (78.2%)
Bulky disease (> 10cm)	104 (31.0%)	109 (32.6%)	95 (30.5%)	101 (33.0%)	87 (29.4%)	99 (33.2%)
Pathology review (n=646)						
DLBCL [#]	288 (85.7%)	292 (87.4%)	269 (86.5%)	269 (87.9%)	269 (90.9%)	269 (90.3%)
Misdiagnosis [†]	21 (6.3%)	19 (5.7%)	19 (6.1%)	15 (4.9%)	5 (1.7%)	7 (2.3%)
No or insufficient material	27 (8.0%)	23 (6.9%)	23 (7.4%)	22 (7.2%)	22 (7.4%)	22 (7.4%)
COO according to Hans (n=411)						
GC	114 (55.6%)	125 (60.7%)	107 (55.2%)	119 (64.3%)	107 (55.2%)	118 (63.8%)
Non-GCB	91 (44.4%)	81 (39.3%)	87 (44.8%)	66 (35.7%)	87 (44.8%)	67 (36.2%)
No or insufficient material	47	33	37	31	37	31
nanosting (n=375)						
GCB	126 (66.3%)	122 (65.9%)	116 (65.9%)	115 (68.0%)	116 (65.9%)	114 (67.5%)
ABC	43 (22.6%)	40 (21.6%)	41 (23.3%)	34 (20.1%)	41 (23.3%)	35 (20.7%)
Unclassified	21 (11.1%)	23 (12.4%)	19 (10.8%)	20 (11.8%)	19 (10.8%)	20 (11.8%)
No or insufficient material	62	54	55	47	55	47
BCL2 expression(n=544)						
≥70%	186 (69.4%)	208 (75.4%)	174 (68.8%)	188 (74.3%)	167 (68.4%)	186 (74.7%)
<70%	82 (30.6%)	68 (24.6%)	79 (31.2%)	65 (25.7%)	77 (31.6%)	63 (25.3%)
No or insufficient material	70	62	60	55	54	51
MYC expression(n=466)						
≥40%	120 (51.7%)	123 (52.6%)	115 (51.6%)	109 (51.2%)	114 (52.8%)	106 (51.0%)
<40%	112 (48.3%)	111 (47.4%)	108 (48.4%)	104 (48.8%)	102 (47.2%)	102 (49.0%)
no or insufficient material	106	104	90	95	82	92
DE MYC/BCL2 (n=454)						
Yes	93 (40.6%)	92 (40.9%)	88 (40.0%)	80 (39.0%)	87 (40.8%)	80 (39.8%)
No	136 (59.4%)	133 (59.1%)	132 (60.0%)	125 (61.0%)	126 (59.2%)	121 (60.2%)
no or insufficient material	109	113	93	103	85	99
Chemotherapy						
CHOP	169 (50.9%)	170 (51.4%)	159 (51.1%)	160 (52.3%)	150 (50.7%)	157 (52.7%)
ACVBP	163 (49.1%)	161 (48.6%)	152 (48.9%)	146 (47.7%)	146 (49.3%)	141 (47.3%)
Not treated	4	3	0	0	0	0

† Follicular lymphoma (FL) grade 3B (n=7), FL grade 3A (n=6), FL grade 1-2 (n=7), Follicular lymphoma of undetermined grade (n=2), Nodular lymphocyte predominant Hodgkin lymphoma (n=4), Mantle cell lymphoma – pleomorphic variant (n=2), B-NHL unclassifiable for technical reason (n=7), Angioimmunoblastic T-cell lymphoma (n=1), Atypical Burkitt

lymphoma (n=1), Burkitt lymphoma / leukaemia (n=1) , Precursor B lymphoblastic leukaemia / lymphoma (n=1), anaplastic large cell lymphoma- ALK + (n=1). # DLBCL include DLBCL NOS, PMBL, EBV DLBCL, High grade B-cell lymphoma double hit or High-grade B-cell lymphoma NOS, T-cell rich B-cell lymphoma

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Table 2: interim-PET results according to the central review in the ITT population

	Obinutuzumab			Rituximab		
	CHOP (n=171)	ACVBP (n=165)	All (n=336)	CHOP (n=172)	ACVBP (n=162)	All (n=334)
PET2						
Negative	111 (64.9%)	111 (67.3%)	222 (66.1%)	103 (59.9%)	103 (63.6%)	206 (61.7%)
Positive	43 (25.1%)	37 (22.4%)	80 (23.8%)	55 (32.0%)	41 (25.3%)	96 (28.7%)
Not reviewed	17	17	34	14	18	32
PET4						
Negative	133 (77.8%)	127 (77.0%)	260 (77.4%)	123 (71.5%)	110 (67.9%)	233 (69.8%)
Positive	18 (10.5%)	19 (11.5%)	37 (11.0%)	32 (18.6%)	24 (14.8%)	56 (16.8%)
Not reviewed	20	19	39	17	28	45

Table 3: 2y-EFS according to treatment arm in the ITT population

		Obinutuzumab			Rituximab		
		N	2y-EFS (%)	95%CI	N	2y-EFS (%)	95%CI
Unstratified EFS		336	59.8	54.3-64.8	334	56.6	51.1-61.8
Stratified EFS							
aaiPI1	CHOP	74	62.2	50.1-72.1	73	58.8	46.7-69.1
	ACVBP	76	60.3	48.4-70.3	74	61.9	49.8-71.9
aaiPI2-3	CHOP	97	56.7	46.2-65.8	99	51.9	41.6-61.3
	ACVBP	89	60.6	49.6-69.9	88	55.7	44.7-65.3

Table 4: Factors influencing patient's outcome

Risk factors	n (%)	2y-PFS % (95%CI)	PFS				OS					
			Univariate analysis		Multivariable analysis		Univariate analysis		Multivariable analysis			
			HR (95%CI)	p	HR (95%CI)	p	2y-OS % (95%CI)	HR (95%CI)	p	HR (95%CI)	p	
Age	>50 y	272 (41%)	82 (76.8-86.1)	1.17 (0.8 – 1.6)	0.36			89.9 (85.5-93.0)	1.42 (0.9-2.2)	0.13		
	≤50 y	398 (59%)	83.9 (79.9-87.1)					92.1 (89.0-94.4)				
Gender	Male	373 (56%)	82.4 (78.1-85.9)	1.17 (0.8 – 1.6)	0.36			91.9 (88.5-94.3)	0.96 (0.6-1.5)	0.88		
	Female	297 (44%)	84 (79.3-87.7)					90.5 (86.4-93.4)				
ECOG	≥ 2	94 (14%)	74.1 (63.9-81.8)	1.68 (1.1-2.5)	0.021			84.1 (74.6-90.3)	2.22 (1.3-3.7)	0.005		
	0-1	575 (86%)	84.5 (81.3-87.3)					92.4 (89.8-94.3)				
Ann Arbor stage	III-IV	552 (82%)	80.6 (77.0-83.7)	3.78 (1.8-7.7)	<0.001	3.71 (1.7-8.0)	<0.001	89.5 (86.6-91.9)	8.62 (2.1-35.3)	<0.001		
	I-II	118 (18%)	94.9 (89.0-97.7)					99.1 (94.0-99.9)				
LDH	Elevated	487 (73%)	83.6 (80-86.6)	0.94 (0.6-1.4)	0.73			91.0 (88.0-93.2)	1.16 (0.7-2.0)	0.57		
	Normal	183 (27%)	81.7 (75.3-86.6)					92.1 (86.9-95.2)				
aa-IPI	2-3	383 (58%)	80.8 (76.4-84.4)	1.46 (1.0-2.1)	0.034			88.8 (85.0-91.6)	2.07 (1.2-3.5)	0.003	3.91 (1.7-8.8)	0.001
	0-1	282 (42%)	86 (81.3-89.6)					94.5 (91.0-96.6)				
Bulk	≥10cm	213 (32%)	78.3 (72.1-83.3)	1.42 (1.0-2.0)	0.05	1.49 (1.0-2.2)	0.039	89.2 (84.0-92.7)	1.45 (0.9-2.3)	0.12		
	<10cm	457 (68%)	85.4 (81.7-88.3)					92.2 (89.3-94.4)				
Hans Score	non GC	250 (47%)	81.9 (76.6-86.2)	1.15 (0.8-1.7)	0.46			89.6 (85.0-92.9)	1.39 (0.8-2.3)	0.20		
	GC	282 (53%)	83.9 (79-87.7)					93.0 (89.3-95.5)				
BCL2	≥70%	391 (73%)	80.6 (76.3-84.2)	1.99 (1.2-3.3)	0.004			90.6 (87.2-93.2)	1.84 (0.9-3.6)	0.064	2.41 (1.0-5.7)	0.047
	<70%	148 (27%)	89.7 (83.5-93.7)					94.3 (89.0-97.1)				
MYC	≥40%	241 (52%)	81.3 (75.8-85.7)	1.39 (0.9-2.1)	0.12			89.8 (85.1-93.0)	1.31 (0.7-2.3)	0.34		
	<40%	221 (48%)	86.2 (80.8-90.1)					92.9 (88.5-95.7)				
DE Myc/Bcl2	yes	183 (41%)	79.8 (73.2-84.9)	1.46 (0.96-2.2)	0.075			88.7 (83.1-92.6)	1.41 (0.8-2.5)	0.23		
	no	267 (59%)	85.9 (81.1-89.6)					92.6 (88.6-95.2)				
Treatment arm	Obinutuzumab	336 (50%)	83.2 (78.7-86.8)	1.03 (0.7-1.4)	0.87	0.95 (0.7-1.4)	0.77	90.7 (87.0-93.4)	0.96 (0.6-1.5)	0.86	0.89 (0.5-1.6)	0.69
	Rituximab	334 (50%)	83 (78.5-86.7)					91.8 (88.1-94.3)				
Chemotherapy	CHOP	339 (51%)	82.7 (78.2-86.4)	1.14 (0.8-1.6)	0.46	1.06 (0.7-1.5)	0.76	92.0 (88.4-94.5)	1.10 (0.7-1.8)	0.70	0.85 (0.5-1.5)	0.59
	ACVBP	324 (49%)	84.7 (80.3-88.2)					91.6 (87.9-94.2)				
PET2/PET4	PET4+	93 (16%)	62 (51.3-71.0)	3.44 (2.3-5.1)	<0.001	3.17 (2.1-4.7)	<0.001	83.1 (73.0-89.7)	2.49 (1.4-4.5)	0.005	3.61 (1.9-6.8)	<0.001
	PET2- or PET+/PET4-	493 (84%)	89 (85.8-91.4)					94.5 (92.1-96.3)				

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Figure 1: Study design

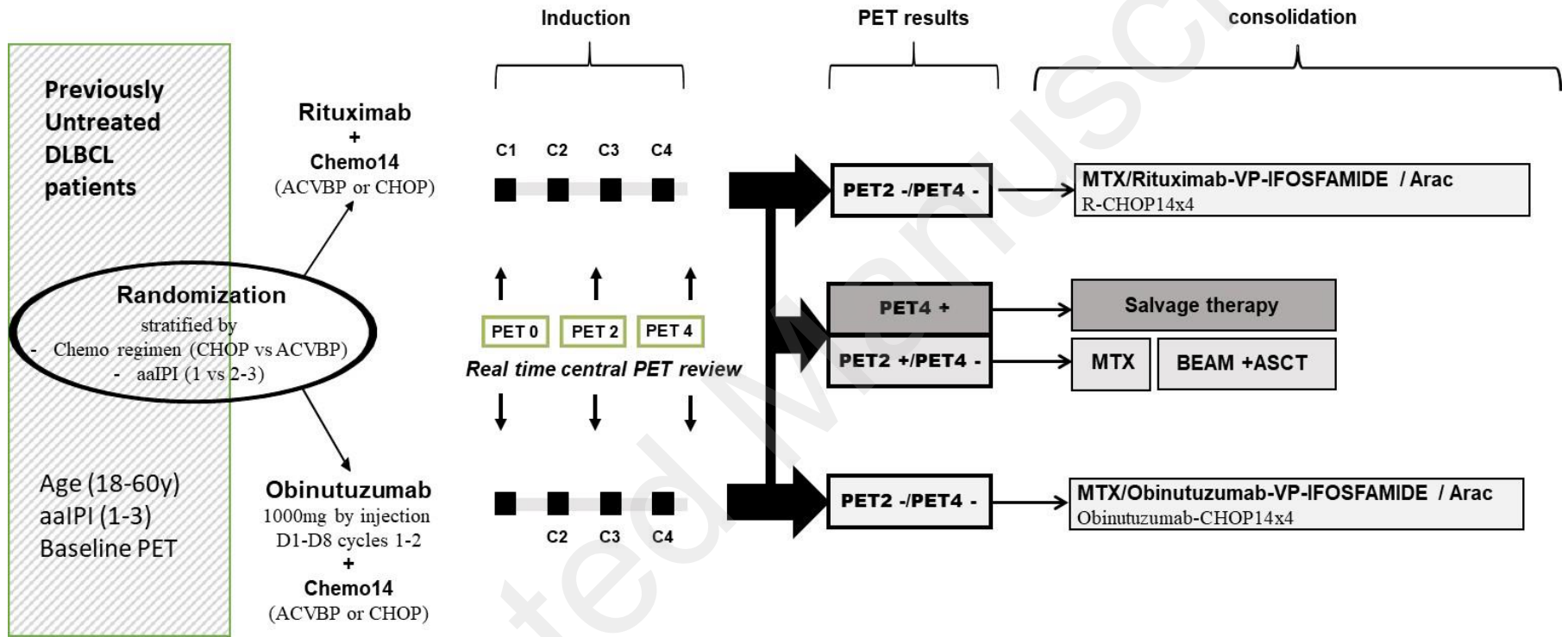
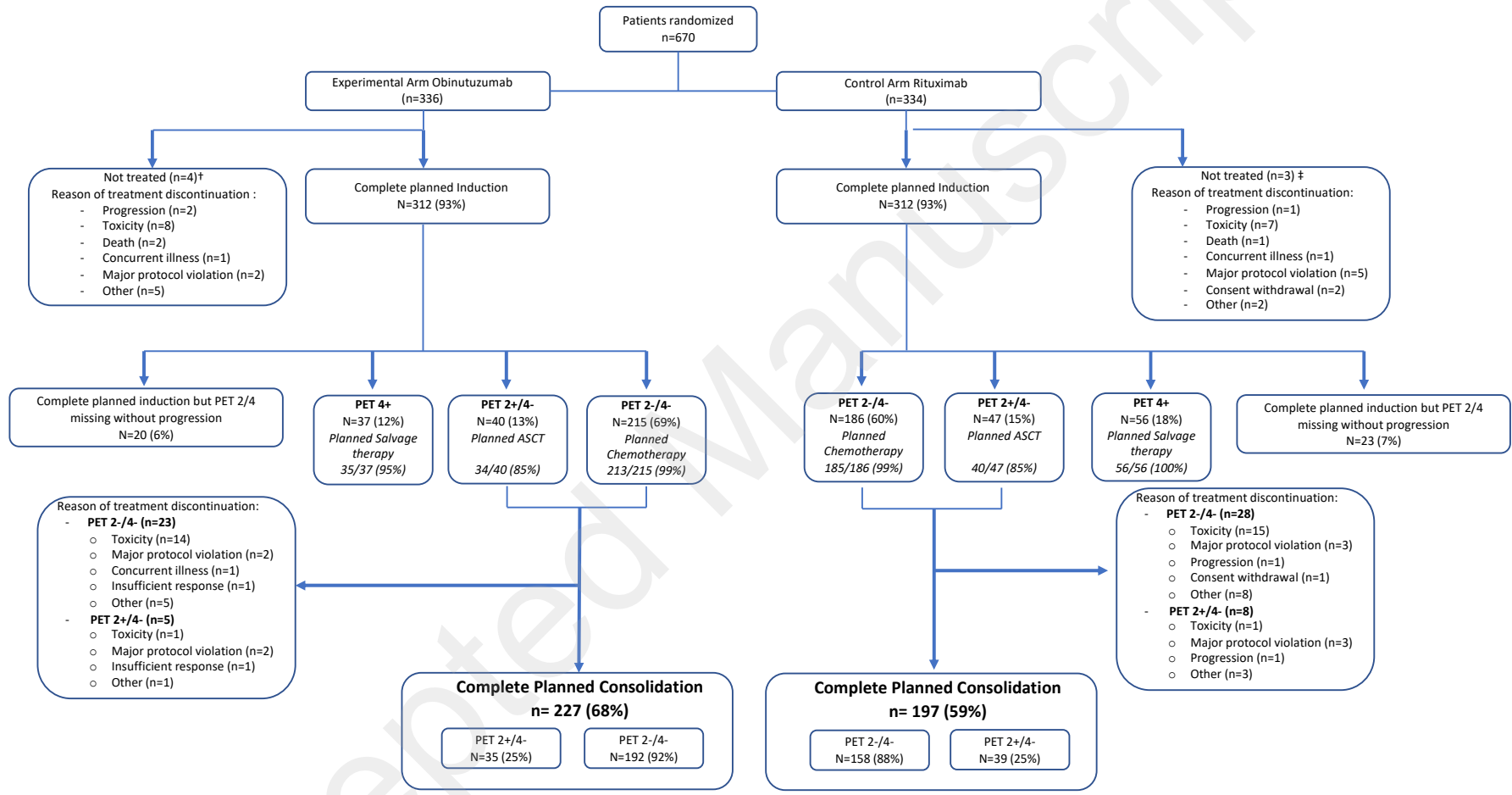


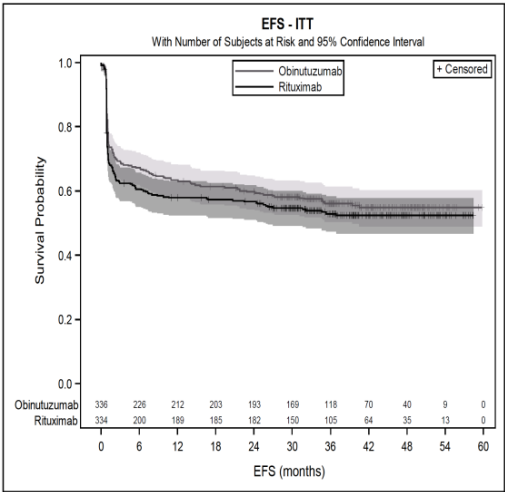
Figure 2 : Flow chart



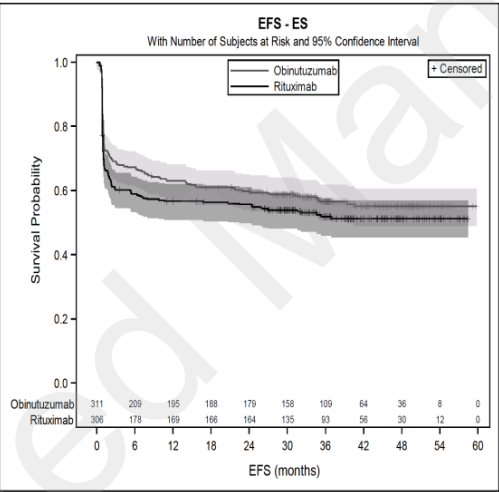
† Major protocol violation (Cerebral lymphoma) (n=1), Concurrent illness (Septic thrombophlebitis due to Staphylococcus aureus) (n=1), Evolution of Lymphoma before treatment (n=1), Misdiagnosis (Acute Leukaemia) (n=1)
‡ Major protocol violation (CNS involved) (n=1), Death (n=1), Evolution of Lymphoma before treatment (n=1)

Figure 3: EFS in ITT (a), ES (b), and PP (c) populations

3 A



3 B



3 C

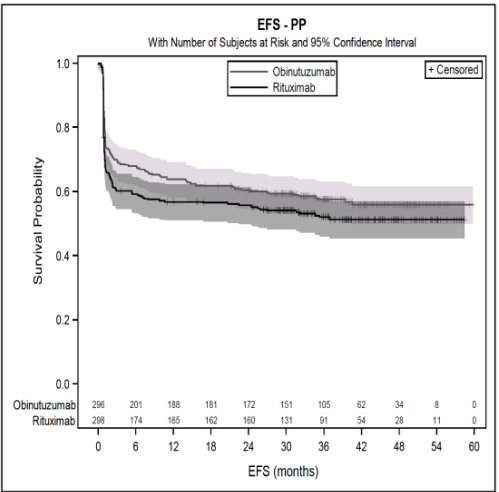
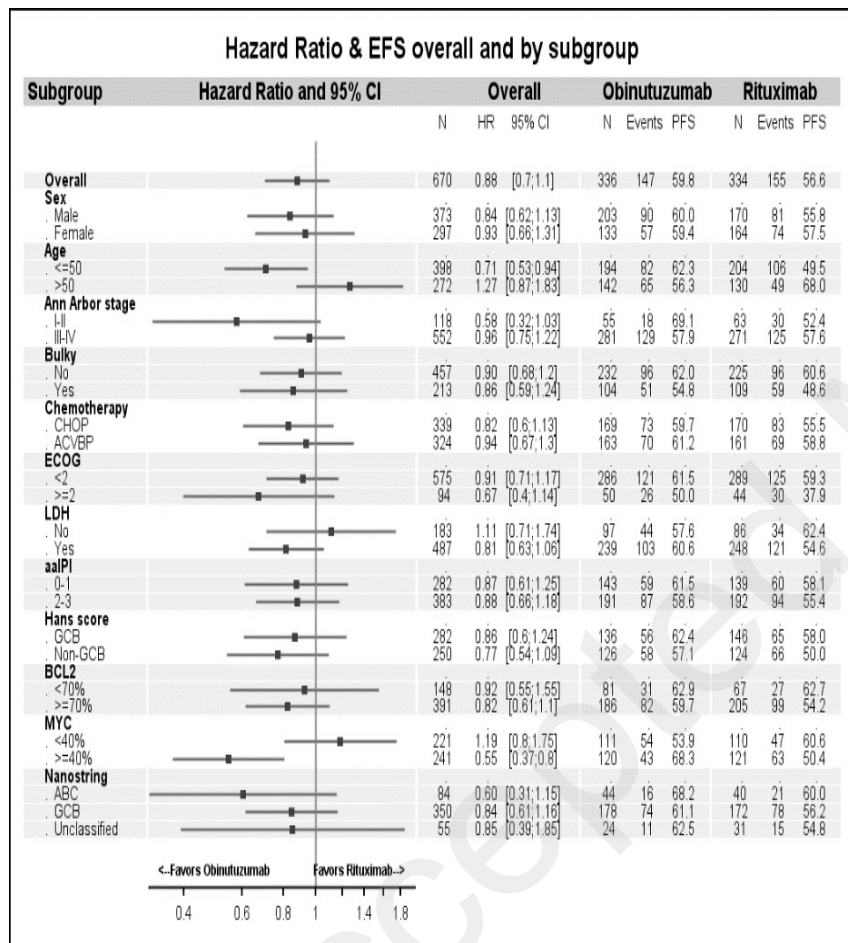


Figure 4: Unstratified Hazard ratio for EFS (panel A) and PFS (panel B) in predefined subsets of patients

A



B

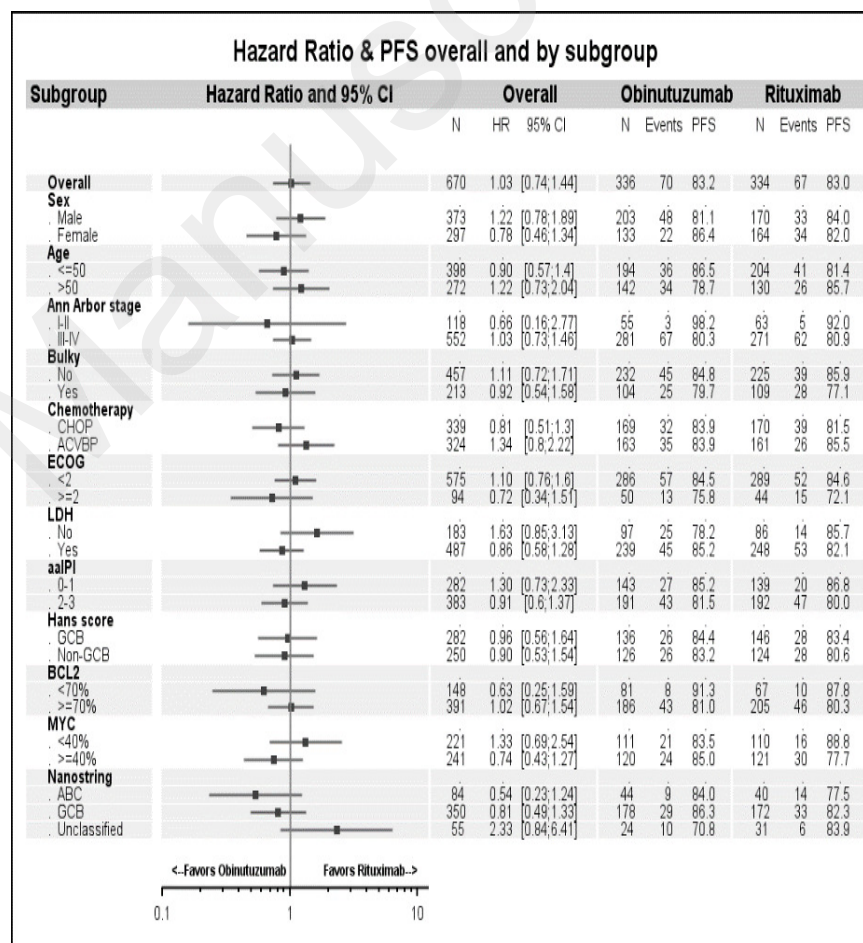
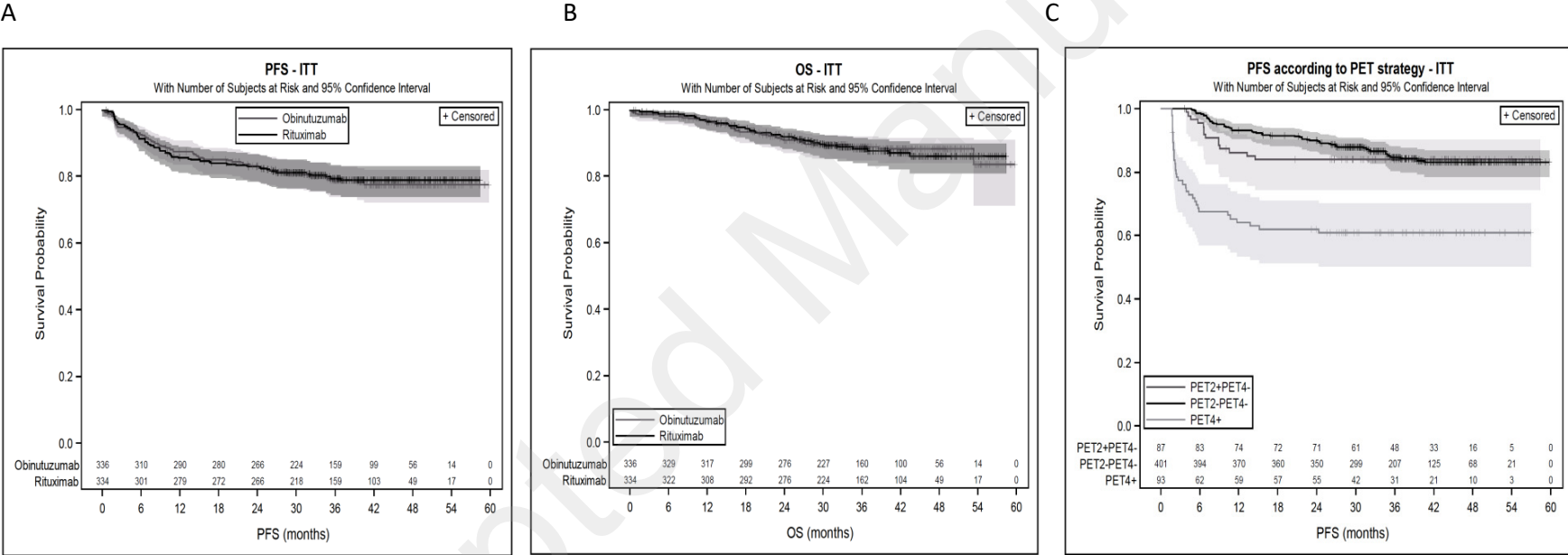
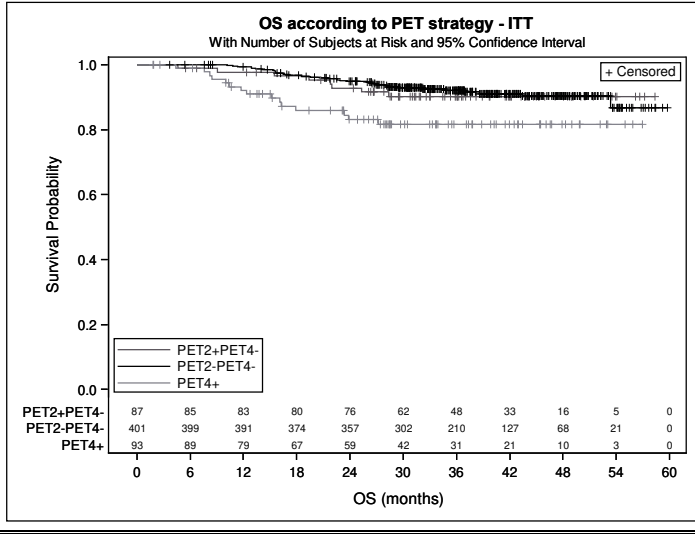


Figure 5 : Unstratified PFS according to randomization arms (A); unstratified OS according to randomization arm (B); PFS according to PET2 and PET4 responses in the whole cohort (C), OS according to iPET response (D)



D



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