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Molecular Response after Obinutuzumab plus High-Dose Aracytine Induction for Transplant Eligible Patients with Untreated Mantle-Cell Lymphoma, a Phase 2 Trial of the LYSA group

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Prior presentations: The main results from the LyMa-101 study were presented orally at the European Hematology Association (13-16 June 2019, Amsterdam-Netherland) and Lugano ICML (18-22 June 2019, Lugano-Switzerland) annual meetings.

SUMMARY

Background. Obinutuzumab monotherapy showed promising efficacy in mantle-cell lymphoma (MCL). We investigated obinutuzumab plus aracytine-containing chemotherapy (O-DHAP) in MCL.

Methods. The LyMa-101 is a single-arm, open-label, multi-center, phase 2 trial done in France. Newly-diagnosed transplant-eligible MCL patients (18 years to <66yrs) received 4 courses of O-DHAP (obinutuzumab 1g iv day1,8 and 15 at cycle 1 and day 1 at each cycle; dexamethasone 40 mg days 1–4, aracytine 2 g/m^2 iv every 12h at day 2 plus cisplatin 100 mg/m^2 iv on day 1 or carboplatin area under the curve = 5 or oxaliplatin 130mg/m2) delivered every 3 weeks before transplantation, a 3-year obinutuzumab (1g every 2 months) maintenance followed by MRD-based obinutuzumab on-demand maintenance. The primary endpoint was minimal residual disease negativity (MRD-neg) in the bone marrow (BM) by qPCR after end of induction (after 4 cycles of O-DHAP) for BM MRD response-evaluable patients (efficacity set, ES). O-DHAP would be considered to be effective if BM MRD-neg was ≥ 70% by intention to treat. LyMa-101 is close for inclusion and registered on clinical trial gov, NCT02896582

Findings. From 29th Nov 2016 to 2nd May 2018, eighty-six patients were enrolled, 81 completed induction, 72 underwent ASCT and 69 started maintenance. BM MRD in the ES (n=73) was negative in 55 cases (75.3%), positive in 12 cases (16.4%) and not evaluated in 6 (8.2%) patients, including 2 with primary resistance. Complete response after 4 O-DHAP, according to Lugano criteria, was 78.8% (95% CI, 68.6 to 86.9) (n=85). The most common grade 3–4 treatment-emergent adverse events (TEAEs) were anemia (grade 3, 26 (30.6%); grade 4, 3 (3.5%) of 86 patients) and neutropenia (grade 3, 13 (15.3%) ; grade 4, 32 (37.6%) of 86 patients). There were no treatment-related deaths during O-DHAP.

Interpretation. O-DHAP is an attractive well-tolerated regimen that provides a high response rate at the molecular level in transplant-eligible MCL patients.

Funding. Roche SAS.

RESEARCH IN CONTEXT

Evidence before this study

Rituximab, a CD20 monoclonal antibody, plus chemotherapy enhances response rates and duration in Mantle-cell lymphoma. Rituximab maintenance prolongs event-free survival after autologous-stem cell transplantation. obinutuzumab is a glycoengineered, type II, anti-CD20 monoclonal antibody designed to improve the antibody-dependent cell mediated cytotoxicity compared to Rituximab. Obinutuzumab is approved in frontline and relapsed/refractory follicular lymphoma but is not superior to Rituximab in diffuse large B-cell lymphoma. We searched Medline up to April 1, 2020 for papers reporting either prospective trials of obinutuzumab for mantle-cell lymphoma, with the search terms "Mantle-cell lymphoma", "obinutuzumab", "Minimal residual disease", with no language restriction. No phase 2 nor 3 investigating obinutuzumab in Mantle-cell lymphoma has been reported, although one phase 2 trial investigated obinutuzumab monotherapy in various relapsed non-Hodgkin's lymphomas, including 15 Mantle-cell lymphoma patients and showed efficacy. There is no published data about obinutuzumab in combination with chemotherapy in Mantle-cell lymphoma and no published data on obinutuzumab in previously untreated Mantle-cell lymphoma patients. Preclinical lab studies with Mantle-cell lymphoma cell lines showed that obinutuzumab can overcome micro-environment-driven Mantle-cell lymphoma cell resistance to targeted drug therapies, such as venetoclax or Ibrutinib. Minimal residual disease in Mantle-cell lymphoma, assessed in peripheral blood and/or bone marrow, has been shown in several phase 2 or 3 prospective clinical trials to be predictive of patient outcome but there are questions regarding most predictive time points and the relative value of peripheral blood versus bone marrow assessment. Minimal residual disease is classically quantified using real-time quantitative PCR of clonal Immunoglobulin or BCL1-IGH rearrangements, but most positive results are below the level of robust, quantitative positivity, so the technique is increasingly challenged by alternative techniques, such as digital droplet PCR or next-generation sequencing, reported to provide more robust quantitation at low levels of positivity.

Added value of this study

The primary endpoint of the LyMa-101 was to evaluate front line molecular negativity after 4 cycles of high-dose aracytine plus obinutuzumab in MCL patients who were molecular response-evaluable at diagnosis (classically approximately 85% of patients included in trials). Since all results were analysed on an intention-to-treat basis, the LyMa-101 study provides major findings in terms of safety and efficacy of obinutuzumab in MCL, including for molecular-response non-evaluable patients. Given the importance of CD20 antibodies in MCL, the LyMa-101 could position obinutuzumab as an alternative to rituximab and lay the foundations for a front-to-front comparison between the two antibodies. More broadly, high-dose aracytine based chemotherapy regimen are common practice in relapsed B-cell lymphomas (including follicular lymphoma and diffuse large B-cell lymphoma):. so the LyMa-101 now provides important data for other B-cell lymphomas.

Implication of all available evidence

Based on the LyMa-101 trial results, obinutuzumab challenges Rituximab in treatment-naïve patients with mantle-cell lymphoma who are frontline transplant-eligible. The LyMa-101 study compares favourably to previous phase 2 and 3 trials including frontline autologous transplantation, raises the question of the best anti-CD20 antibody for mantle-cell lymphoma patients and reinforces the interest of early surrogate markers, such as minimal residual disease. Such markers could be used to identify patients who do not respond well to chemotherapy and thus might be candidates for alternative approaches at a much earlier stage.

INTRODUCTION

Mantle-cell lymphoma (MCL) is an aggressive B-cell malignancy with a poor prognosis. High-dose aracytine plus Rituximab-containing chemotherapy regimens followed by autologous stem-cell transplantation (ASCT) and rituximab maintenance is standard of care for transplant-eligible patients.[1,2] Obinutuzumab is a glycoengineered, type II, anti-CD20 monoclonal antibody designed to improve antibody-dependent cell mediated cytotoxicity compared to Rituximab. Obinutuzumab is approved in frontline and relapsed/refractory (R/R) follicular lymphoma but is not superior to Rituximab in diffuse large B-cell lymphoma. *In-vitro* experiments suggest that obinutuzumab provides better anti-MCL activity than Rituximab.[3] Little *in-vivo* data are available regarding obinutuzumab in R/R MCL patients and there is no published data about obinutuzumab in treatment-naïve patients.[4]

Real time quantitative PCR (q-PCR) is the gold-standard technique for minimal residual disease (MRD) quantification in MCL. A clonal Immunoglobulin or BCL1-IGH tumor marker can be identified in more than 80% of MCL patients (so-called informative patients), who are eligible for MRD assessment. Several trials demonstrated the prognostic value of MRD status, with MRD negative (MRD-neg) patients having a significantly better outcome.[1,5,6] At end of therapy, patients with MRD negativity benefit from more prolonged control of disease than MRD positive patients. End of treatment is, however, too late to adapt the therapeutic strategy, since some, potentially inappropriately treated, patients will relapse before. MRD assessment at end of induction and before autograft is a better timepoint to identify a maximum number of high-risk patients.[1,5] MRD in MCL can be measured in the peripheral blood (PB) or bone marrow (BM). Its predictive value is independent of induction chemotherapy and it reflects induction efficacy.

In the LyMa-101 trial, obinutuzumab was associated with DHAP (O-DHAP), a high-dose aracytine and platinum-based regimen. Its primary objective was to investigate O-DHAP efficacy, measured by MRD qPCR status in the BM after 4 courses of O-DHAP.

METHODS

Study design and participants

The LyMa-101 study (NCT02896582; EudraCT2016-000548-33) is a prospective, open phase 2 trial testing the effect of O-DHAP in untreated MCL patients eligible for intensive therapy. The study started in 29th November 2016. Participants were enrolled from 28 centers in France. The study was approved by an independent ethics committee, in accordance with the Declaration of Helsinki and Guidelines for Good Clinical Practice. All patients gave written informed consent.

MCL patients presenting with the following key inclusion criteria were eligible: age > 18 and under 66 years; untreated transplant-eligible patients with histologically confirmed MCL according to the WHO classification[7]; Ann Arbor stage II-IV; WHO performance status of <3; life expectancy more than 3 months; BM aspirate at diagnosis for MRD assessment. Patients with the following comorbidities were excluded: severe cardiac disease (NYHA grade 3-4); chronic or impaired liver function (ALAT/ASAT ≥ 2.5ULN, bilirubin ≥ 1.5ULN), renal (calculated creatinine clearance < 50ml/min) or other organ function which will interfere with the treatment if not related to lymphoma; hepatic veno-occlusive disease (VOD) or sinusoidal obstruction syndrome ; absolute neutrophils count <1.5 x 10^9/L or platelet counts 75 x 10^9/L not related to BM infiltration ; pregnancy ; known seropositivity for HIV, HCV or other active infection uncontrolled by treatment; viral infection with hepatitis B virus defined as hepatitis B surface antigen positive and/or hepatitis B core antibody positive; prior history of progressive multifocal leukoencephalopathy; vaccination with a live vaccine a minimum of 28 days prior to inclusion; history of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies.; known sensitivity or allergy to murine products ; psychiatric illness; person deprived of his/her liberty by a judicial or administrative decision or hospitalized without consent or under legal protection (appendix; page 7). All biopsies were centrally reviewed (LYSA-P, France). Ki67 and TP53 expression was assessed centrally by immunohistochemistry (IHC) and bioMIPI was calculated.[8] TP53 mutations were detected by next-generation sequencing (NGS) of QiaSEQ (Qiagen) DNA libraries from PB/BM samples with at least 1% infiltration, as quantified by ddPCR and/or flow cytometry, or as described[9]

Procedures

In this phase 2 multicenter, single-arm study, treatment included 4 phases: induction, consolidation, maintenance and post-maintenance. The study design and treatment schedule are shown in the appendix (page 2 and 9). The primary endpoint (eg MRD in BM at end of induction) was performed centrally in two reference laboratories (Creteil and Necker Hospitals, France) and borderline results discussed between them. Induction consisted of 4 cycles of O-DHAP before ASCT consolidation followed by obinutuzumab maintenance for 3 years then obinutuzumab on-demand for MRD positive patients as post-maintenance. The O-DHAP regimen (obinutuzumab 1000 mg/m^2 intravenously on day 1, 8 and 15 at cycle 1 and day 1 at cycle 2, 3 and 4; dexamethasone 40 mg intravenously on days 1–4, aracytine 2 g/m^2 intravenously every 12 h on day 2, and according to local investigator: cisplatin 100 mg/m^2 by continuous infusion over 24 h on day 1 or carboplatin area under the curve = 5 or oxaliplatin 130mg/m^2) was delivered every 21 days. Following French health authorities recommendations, use of oxaliplatin was not allowed in last revised version of the protocol because VOD occurred in an unrelated phase IB trial (NCT02055924) where a BTK inhibitor was added to DHA-oxaliplatin regimen. Any case of VOD has been reported in the LyMa-101 trial. For patients in response, the

conditioning regimen for ASCT was O-BEAM (obinutuzumab (1000mg/m^2 at D-8) plus BEAM (carmustine [1,3-bis(2-chloroethyl)-1-nitrosourea] 300mg/m^2 D-7, etoposide 400mg/m^2/d from D-6 to D-3; aracytine 400mg/m^2/d from D-6 to D-3 and melphalan 140mg/m^2 at D-2)). The maintenance schedule was 1000 mg/m^2 intravenous obinutuzumab once every 2 months for 3 years. After 3 years of maintenance, the therapeutic scheme for MRD positive patients was one injection of obinutuzumab at D1, 8 and 15 of the first month and then once every month until MRD negativity, plus one additional injection after the last MRD negative sample. Obinutuzumab dose reduction was not permitted.

At diagnosis, clonal immunoglobulin heavy chain gene rearrangement (IGH VDJ) and/or BCL1-IGH rearrangements were sequenced from PB or BM DNA in order to design allele-specific-oligonucleotide (ASO) primers for quantification of MRD. Droplet digital (dd)PCR was used at diagnosis to quantify the tumor mass (in addition to flow cytometry)[10] and to determine the first point of the qPCR calibration curve. MRD follow-up was performed by ddPCR,[11] for all follow-up, but classical, ASO-based, qPCR MRD quantification was carried out at end-of-induction, using the same ASO primers as for ddPCR [11]. qPCR was performed relative to diagnostic gDNA 10-fold serial dilution calibration curves [12] and interpreted according to Euro-MRD guidelines, using a 1 Ct cut-off from background.[13] The technique allows robust quantification at positivity levels above 0.01%. Samples which were positive but not quantifiable were defined as BQR (below quantitative range). MRD in both PB and BM was assessed at baseline, end of induction (EOI), after ASCT, at the end of the 3-year maintenance, at the end of the MRD-driven "on-demand" post-maintenance period, in case of relapse or progression and at premature discontinuation of treatment. MRD in PB only was assessed every 6 months during the 3 years of obinutuzumab maintenance and every 3 months during the 3 years of the obinutuzumab MRD-driven « on-demand » phase.

TP53 was analysed by NGS in relapsed patients samples with at least 1% infiltration at diagnosis, evaluated by ddPCR and/or flow cytometry. QiaSEQ (Qiagen) DNA Libraries were prepared according to the manufacturer's instructions, and sequenced using the Illumina MiSeq sequencing system. Sequencing reads were analysed using in-house software (Polyweb, Institut Imagine, Paris), or the qiaseq pipeline. All coding *TP53* exons were sequenced.

Response by CT-scan and FDG-PET were assessed after 4 courses of O-DHAP, after ASCT and after 3 years of maintenance. Response by CT-scan only was assessed every 6 months during the 3 years of obinutuzumab maintenance then every year during the "on-demand" post-maintenance period.

Safety and other assessments were performed by the investigators.[14] According to protocol, all grade 3, 4 and 5 and all SAEs were reported. Only grade 1 and 2 SAEs were reported. Clinical examination, complete blood cell count and biochemical blood test (including hepatic enzymes, LDH, creatinine, albumin, and ionogram) were performed before a d-1 or D1 of each O-DHAP. Treatment side effects were graded according to the Common Terminology Criteria for Adverse Events (version 3.0). Data were monitored by the LYSARC trial sponsor.

Outcomes

The LyMa-101 primary objective was the efficacy of four courses of O-DHAP (end of induction) measured at the molecular level in BM. Secondary objectives were: clinical response (overall response including CR, CRu and PR) after O-DHAP efficacy (assessed by CT/scan, FDG-PET and MRD) before and after ASCT and every 6 months until the end of the 3-years maintenance period; MRD negativity after the 3-years maintenance and

during the on-demand maintenance periods; FDG-PET results after 3-years maintenance; duration of MRD negativity; PFS and overall survival (OS); incidence of stem cell collection failure after O-DHAP; tolerability of O-DHAP; baseline factors predicting factors for PFS and OS. Patients were removed from the study in case of death, consent withdrawal or if lost to follow up. Herein, we present the result of the primary objective, secondary objectives that require longer follow-up are not presented.

Statistical analysis

Based on interim results of LyMa and EU-MCL younger trials, the BM MRD negativity rate by qPCR after aracytine-containing induction varies from 61 to 65%.[5] We thus hypothesized that induction with O-DHAP would be considered effective if MRD negativity in the BM after four courses of O-DHAP was ≥ 70% (P_1) and ineffective if ≤ 55% (P_0) by intention to treat. Patients who progressed during induction and/or before MRD assessment at end of induction were also considered as MRD positive. Sample size calculation was performed using an exact single-stage phase II design with East 5.4.[15] Taking into-account a 15% drop-out rate, 83 patients should be included (one-sided test, α risk of 0.05, β of 0.20). Assuming that some patients would not receive treatment and/or be non-informative for MRD in BM and/or PB at baseline, enrolment was closed after identification of at least 70 MRD informative patients.

The included set (IS) includes all patients having signed informed consent. The safety set (SS) includes all patients having received at least one dose of obinutuzumab. The efficacy set (ES) includes all MRD-informative (BM and/or PB) patients having received at least one dose of obinutuzumab. The data cut-offs were 27th Aug. 2018 for induction and 21th Nov 2018 after ASCT. All outputs were produced using SAS version 9.3 and AdClin version 3.3.3. The LyMa-101 study is registered on clinical trial gov. (NCT02896582) and clinicaltrialsregister.eu (EudraCT2016-000548-33)

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Overall, 86 patients were included between 29th Nov 2016 to 2nd May 2018 (Table 1). Sixty-three (73.3%) of 86 patients were male and median age was 58 years (IQR, 51-62). MIPI and MIPI-b risk scores were low in 47 (54.7%) and 13 (16.1%) cases, intermediate in 24 (27.9%) and 40 (49.4%) cases and high in 14 (16.3%) and 28 (34.6%) cases. Fifteen (17.4%) of 86 patients presented with a blastoid variant. All but 2 patients presented with advanced disease (stage III or IV) at diagnosis median time from diagnosis to start of induction was 1.1 month (0.7-1.7, IQR 0.7-1.7). The patient flow chart is presented in Figure 1. At first cycle, 8 (9.41%) patients received cisplatin (among whom three changed to carboplatin and two to oxaliplatin during induction), 35 (41.18%) carboplatin and 42 (49.41%) oxaliplatin (among whom one changed to cisplatin and three to carboplatin during induction). Two patients progressed during induction, 73 were transplanted and 69 patients started obinutuzumab maintenance.

Regarding the primary objective (MRD negativity in BM at end of induction), 73 patients had a detectable IGH VDJ and/or BCL1-IgH clone in BM and/or PB at baseline (ES). Twelve patients (14%) out of 85 were not evaluable for MRD, essentially due to purely nodal disease with no detectable MCL clone in PB or BM. Mean infiltration, quantified by ddPCR was 24% (range 0.06-100%) in BM and 20% (range 0.4-93%) in PB. Three patients stopped before EOI because of AEs (peritonitis, infusion related syndrome and febrile neutropenia, one each) and BM evaluation in a fourth failed for technical reasons. Two patients progressed before EOI. The remaining 67 patients had BM assessment at EOI. Twelve patients were BM MRD pos, including 3 with quantifiable positivity above 1E-04/0.01% and 9 with low level positivity BQR (Table 2). Among these 12 patients, MIPI score at diagnosis was low in 7 cases, intermediate in 3 cases and high in 2 cases. Two patients out of the 12 with BM positivity also demonstrated a BQR)clone in the PB. In all, 14 out of 73 patients (19.2%; BM pos. in 12 cases plus 2 patients who progressed during induction) did not achieve clinical or molecular CR at EOI. Conversely, 55 (75.3%) out of 73 patients of the ES reached MRD negativity in BM at EOI. Of note, one BM neg patient was PB positive BQR, with confirmation of the PB positivity (1E-5) but BM negativity by ddPCR. This patient did not show any clinical/histological high-risk features. As such 15 (20.54%) patients out of 73 in the ES were MRD positive in BM and/or PB. Among patients with MRD quantification in BM at EOI (this excludes the six patients with no BM MRD assessment at EOI), 55 (82%) out of 67 reached BM MRD negativity (Figure 2).

At EOI, overall response (CR, CRu and PR) rate in the SS set (n=85) was 91.7% including 52 (61.1%) patients who reached CR/CRu. According to Lugano criteria, 67 (78.8%) patients reached CR. There was no stem cell collection failure (median CD34+ was 7.9 10^6/kg; range 2.5-25.5). PFS and OS curves are shown in appendix (page 3). The median Follow-up is 14.6 months (range 3.8-24.4, IQR 10.3-17.2), 93.4% (95% CI, 84.7 to 97.2) of patients remaining progression-free at 12 months. OS rate was 96% (95% CI, 88.1 to 98.7) at 12 months. None of the 12 MRD positive patients have relapsed, to date, and the only patient who has so far progressed was MRD negative in BM and PB at end of induction. *TP53* was abnormal by NGS and/or IHC in 2/13 MRD pos. cases (appendix p12) including the single PB+/BM- patient. Of the 3 patients with resistance/early progression, one was TP53 mutated by NGS, a second TP53 positive by IHC and the third Ki67 positive by IHC. As such, all three had day one high-risk features.

The safety data during induction are presented in Table 3. Main reasons for stopping treatment before ASCT were adverse events. Thrombocytopenia grade 4 was reported in 49 (58%) patients out of 85. Tumor lysis

syndrome of grade 3 was reported in 3 patients and a grade 4 infusion related reaction in 2 patients. Fifty-eight (55.2%) SAEs occurred during the induction phase. Two patients had renal failure; both had received cisplatin. Most frequent SAEs during induction were infection (n=8); GI (n=5) and general disorders with fever (n=5). Obinutuzumab was discontinued during induction in 28 patients who presented 74 AEs among whom 43 in 21 patients were obinutuzumab-related. All AEs leading to obinutuzumab discontinuations occurred during cycle 1 and main reasons were grade 3 or 4 thrombocytopenia in 19 patients (25.7%) (all SAEs, AEs responsible for treatment discontinuation and obinutuzumab interruption during induction are listed in appendix page 13, 15 and 16). Overall, 25 AEs (13 during induction, 5 during ASCT and 7 during maintenance) in 14 patients led to treatment discontinuation, including 5 cases during induction. At last update, nine patients have stopped the maintenance phase (medical decision, death, myelodysplasia, myeloproliferative neoplasm and progression -one case each; 4 AEs in 4 cases). Three patients died (MCL, myocardial infarction and intra cerebral haemorrhage); neither were related to obinutuzumab.

DISCUSSION

The LyMa-101 trial is a large study that addresses the question of obinutuzumab in MCL. Its endpoint was BM MRD negativity rate after 4 courses of O-DHAP (end of induction). The MRD negativity rate of 75.3% (55/73) is superior to the pre-defined statistical threshold to consider O-DHAP as an effective induction chemotherapy regimen.

The efficacy of obinutuzumab in NHL is heterogeneous. The GADOLIN and GALLIUM trials demonstrated obinutuzumab efficacy in FL.[16,17] In contrast, frontline CHOP plus obinutuzumab in DLBCL failed to demonstrate superiority over R-CHOP.[18] More recently, obinutuzumab has been investigated in association with targeted therapies such as Ibrutinib, Venetoclax or Lenalidomide in both NHL and CLL.[19–24] These trials demonstrated the good safety profile of obinutuzumab, alone or in combination. There is very limited published data on obinutuzumab in MCL. Fifteen R/R MCL patients were enrolled in the obinutuzumab monotherapy GAUGIN trial, four patients responded.[4] There are no published data about obinutuzumab plus chemotherapy in MCL. Frontline treatment guidelines for young, transplant-eligible, MCL patients recommend a high-dose aracytine-containing regimen prior to ASCT.[25] Obinutuzumab has not been investigated in combination with high-dose aracytine-based chemotherapy regimens such as DHAP, one of the more popular treatments for relapsed/refractory DLBCL and treatment-naive MCL. The LyMa-101 trial demonstrates that O-DHAP is feasible and safe in newly diagnosed MCL. AEs and SAEs are comparable to those reported with R-DHAP and are easily manageable in a haematology department. In note, only 8 patients received cisplatin during induction in the present trial.

The overall response rate according to CT-Scan was 91.7% and 78.7% of patients reahed CR according to PET/CT. The 75.3% rate of MRD negativity in the BM at EOI also compares favorably with other induction regimens used routinely such as R-CHOP (26% MRD negativity), RCHOP/RDHAP (61% MRD negativity) or R-DHAP (66% MRD negativity) in younger MCL patients or FCR (67% MRD negativity) and RiBVD (77% MRD negativity) in elderly non-ASCT eligible patients.[1,5,6,26] Of note, the BM MRD-neg rate in these trials was calculated only in chemo-sensitive patients who underwent full chemotherapy induction without major toxicities and had a BM aspirate at EOI (not always mandatory in these trials). The comparable MRD-neg rate in the present trial was 82% (55/67) in BM and 95.5% (63/66) in PB. It can be assumed that MRD negativity rates at EOI are probably overestimated in these trials, in contrast to the LyMA-101 trial, where MRD rate has been calculated on an intention-to-treat basis in all MRD-evaluable patients. Our results show that obinutuzumab requires further investigation in clinical trials.

Pott and colleagues demonstrated that molecular remission is an independent predictor of patient outcome[6] and concluded that MRD assessment might be used to drive medical decisions.[5] We evaluated MRD in BM prior to ASCT because it has been shown to be a good surrogate marker for long term outcome but also because MRD negativity in BM is more difficult to achieve than in PB, thus providing a more stringent evaluation of obinutuzumab efficacy. The predictive value of MRD in BM vs. PB remains an open question, with more published data available for PB than BM analysis and it is prudent to consider patients MRD positive if one or the other is positive. In the present study, MRD in both PB and BM assessment confirms the high response rate following O-DHAP induction. Furthermore, MRD assessment before (but not after) ASCT allows the design of early risk-adapted MRD-driven strategies, as in the EA4151 (NCT03267433) trial. Indeed, in

future trials, novel agents such as Ibrutinib and/or Venetoclax could be added (or not) or ASCT cancelled (or not) according to pre-transplant MRD status.

The secondary aim of the present study is to use PB MRD assessment post-maintenance to start pre-emptive treatment. MRD-based Rituximab on-demand pre-emptive treatment has already been successfully investigated in the MCL-2 prospective trial.[25] The short FU in the LyMa-101 trial and absence of a comparative arm limit conclusions about the predictive value on PFS and OS of EOI or post-ASCT MRD status, the interest of post-maintenance MRD-driven obinutuzumab retreatment or about the impact of O-DHAP.

MRD in MCL is assessed by qPCR-based but most qPCR positive results are BQR, within the 0.001-0.01% range of low-level positivity. The use of qPCR in MCL is therefore increasingly challenged by flow cytometry[27], ddPCR[11] and NGS.[28] Both qPCR and ddPCR are more sensitive than flow cytometry. Given its robust quantification sensitivity down to 0.001% and reduced number of non-quantifiable results compared to qPCR, for the present study, we chose to do ddPCR, complemented by qPCR quantification at EOI for historical comparisons. Two studies with limited number of patients reported 93% (14/15 patients) and 78% (7/9) MRD negativity in PB by NGS in Rituximab and Bendamustine treated younger MCL patients[29,30] compared to 95.5% (63/66) negativity in the present study. Despite limitations in study comparisons, it thus appears that O-DHAP provides high level of BM MRD negativity. The interest and predictive value of early PCR-based MRD assessment also needs to be compared to other techniques, such as interim-PET, NGS or ctDNA monitoring. The interest of an MCL composite score that integrates various technologies into a personalized MCL treatment-risk profiling algorithm based on multi time points or continuous multi-technology response assessments also merits evaluation.

Emergence of novel targeted therapies has modified treatment strategies in R/R MCL patients and they will undoubtedly soon be considered as frontline treatment. The chemotherapy-first dogma in MCL may soon be replaced by a chemo-free first regimen, although long-term follow up with respect to both safety and efficacy will be necessary to assess their respective roles. The role of anti-CD20 antibodies might also be challenged by novel agents. Rituximab maintenance frontline is the only drug that has demonstrated a benefit in OS.[2,26] The tolerance profile of anti-CD20 antibodies, their effectiveness, make them attractive for chemo-free strategies. An anti-CD20 antibody does not only have an additional effect when combined with novel agents, it could increase their efficacy. A pre-clinical *in-vitro* study showed that obinutuzumab overcomes environment-induced venetoclax tumor cell resistance and that an obinutuzumab/venetoclax/ibrutinib combination is very active against MCL.[3] How chemo-free combinations will compare to standard chemotherapy, with or without ASCT, needs to be evaluated in prospective trials in MCL. Early MRD negativity assessment might become a very helpful early surrogate endpoint to compare chemo-free regimens to standard chemotherapy, although it is also possible that MRD might fade in importance as detectable disease persists without symptoms or progression on treatment.

In conclusion, the LyMa-101 trial achieved its primary endpoint and demonstrates the efficacy of O-DHAP as induction chemotherapy, with bone marrow MRD negativity potentially predicting long-term disease control. Longer FU is needed to investigate the MRD-based obinutuzumab on-demand strategy post maintenance.

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DECLARATION OF INTERESTS

Steven Le Gouill, Consulting and advisory board: Roche SAS, Janssen-Cilag, Gilead/kite, Novartis, Loxo, Abbvie, Servier; Asma Beldi-Ferchiou declares no competing interests; Marion Alcantara declares no competing interests ; Victoria Cacheux declares no competing interests; Violaine Safar declares no competing interests; Barbara Buroni declares no competing interests; Stéphanie Guidez declares no competing interests; Thomas Gastinne declares no competing interests; Danielle Canioni declares no competing interests; Catherine Thieblemont, Honoraria: Amgen , Celgene, Jazz Pharma, Kyte/ Gilead, Novartis, Servier, Roche, Janssen; Research funding: Roche, Celgene, Aspira; Hervé Maisonneuve declares no competing interests; Caroline Bodet-Milin, consulting BMS and Gilead ; Roch Houot, honoraria or consulting fees from Bristol-Myers Squibb, MSD, Gilead, Kite, Roche, Novartis, Janssen, and Celgene ; Lucie Oberic, Advisory board: Roche, Takeda; honoraria: Celgene, Janssen, Roche; Krimo Bouabdallah declares no competing interests; Charles Bescond declares no competing interests; Ghandi Damaj, Board : Roche, taked ; Travel : Roche AbbVie Pfizer, Grants : takeda, roche ; Arnaud Jaccard declares no competing interests; Nicolas Daguindau declares no competing interests,; Anne Moreau declares no competing interests; Hervé Tilly, Consulting and advisory board: Roche, Janssen-Cilag, Karyopharm, Astra-Zeneca, Lectures: Roche, Bristol-Myers-Squibb, Servier ; Vincent Ribrag, Infinity Pharmaceuticals, Bristol-Myers Squibb, PharmaMar, Gilead Sciences, AZD, Epizyme, Incyte, MSD, Servier, Roche, arGEN-X BVBA ; Marie-Hélène Delfau-Larue declares no competing interests; Olivier Hermine, Celgene research grant, Alexion research grant, Ab science co founder research grant consulting, Inatherys co founder research gérants; Elizabeth Macintyre: Consulting for Servier.

DATA SHARING

Request for access to the study data can be asked by email to the corresponding author. 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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Tables and Figures

Table 1 Patient baseline demographic and disease characteristics. MIPI=Mantle Cell Lymphoma International Prognostic Index. LD=longest dimension; ECOG=Eastern Cooperative Oncology Group; MRD, minimal residual disease; BM, bone marrow

Table 2 Responses in the efficacity set. * 6 patients not evaluated due to 3 adverse events, 1 technical failure and 2 early progressions; ** one PB pos patient; *** including positivity below the quantitative range; **** both pts with early progression but no MRD assessment were considered positive

Table 3 Patients with at least one event by worst grade of AEs 3 or 4 (no 5 reported) - Safety set (n=85) during induction. AE, adverse event

Figure 1 Patient flow chart. O-DHAP, Obinutuzumab, dexamethasone, high-dose aracytine, salt platinum; AE, adverse event; ASCT, autologous stem-cell transplantation; MPS, myeloproliferative syndrome, MDS, myelodysplasic syndrome; (ES), patients included in the efficacy set

Figure 2 MRD status at diagnosis and at end of induction. Minimal residual disease (MRD) status by ddPCR at diagnosis and qPCR at end of induction (end ind., after 4 cycles of O-DHAP) in peripheral blood (PB) and bone marrow (BM). MRD values positive below quantitative range (BQR) were separated into those with one, two or 3 positive triplicate results.

Figure 1. Patient flow chart

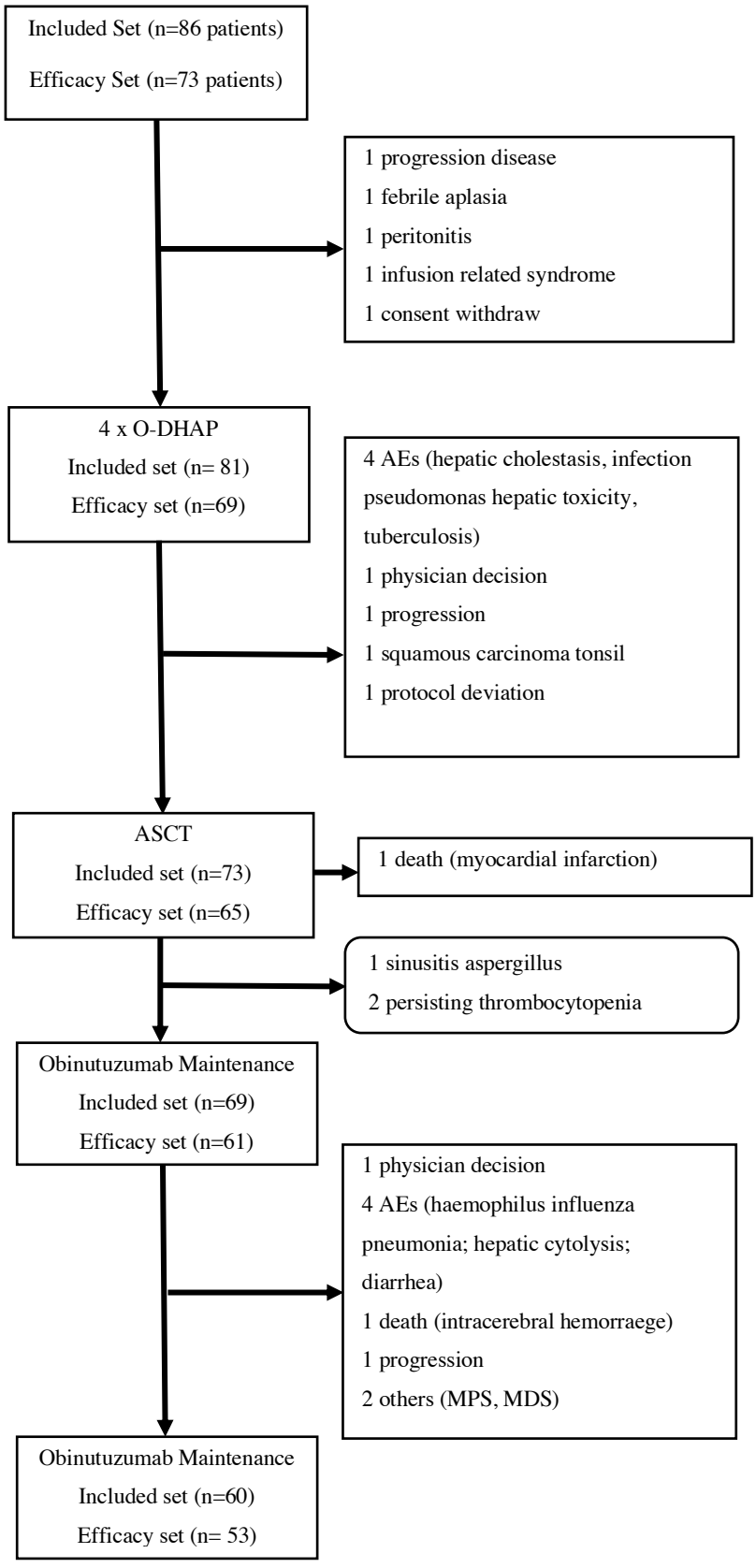


Table 1: Patient baseline demographic and disease characteristics

	All patients (n=86)
Median age (range), years	58 (32 to 65)
Male, n (%)	63 (73.3%)
Ann Arbor stage at diagnosis, n (%)	
II	2 (2.3%)
III	6 (7%)
IV	78 (90.7)
Simplified MIPI, n (%) *(missing = 1)*	
Low risk (1 to 3)	47 (54.7%)
Intermediate risk (4 to 5)	24 (27.9%)
High risk (6 to 11)	14 (16.3%)
Simplified bio-MIPI, n (%) *(missing= 5)*	
Low risk (1 to 3)	13 (16.1%)
Intermediate risk (4 to 5)	40 (49.4%)
High risk (6 to 11)	28 (34.6%)
ECOG performance status, n (%)	
0	55 (64%)
1	27 (31.4%)
2	4 (4.7%)
Bulky disease	
≥5 cm, n (%)	35 (40.7%)
≥10 cm, n (%)	7 (8.1%)
BM involvement (biopsy or aspirate), n (%):	
Involved	
Not involved	66 (77.5)
Not evaluable	16 (19)
	3 (3.5)

Histology, n (%) – centraly reviewed) Blastoid	 15 (17.4%)
Ki67% pos cells *> 30%* *Median (range)*	 29 (33.7%) 30 (0 to 95)
Patients suitable for MRD monitoring in BM, n (%)	73 (84.9)

Table 2. Responses in the efficacity set

Bone Marrow MRD evaluation by qPCR at end of induction in the efficacity set (n=73)

	Total (n=73)	%
BM assessed by qPCR *	67	91.8
BM MRD negative**	55	75.3
BM MRD positive ***	12	16.4
Patient considered MRD pos ****	14	19

Table 3 Patients with at least one AE before the end of induction by worst grade 3, 4 and 5 plus grade 1 and 2 SAEs - Safety set

System Organ Class Preferred Term	Safety Set n=85							
	Grade 1 n=3		Grade 2 n=6		Grade 3 n=57		Grade 4 n=62	
AEs	**3**	**(3.5%)**	**6**	**(7.1%)**	**57**	**(67.1%)**	**62**	**(72.9%)**
blood and lymphatic system disorders	**0**	**(0.0%)**	**1**	**(1.2%)**	**46**	**(54.1%)**	**59**	**(69.4%)**
thrombocytopenia	0	(0.0%)	0	(0.0%)	8	(9.4%)	49	(57.6%)
neutropenia	0	(0.0%)	0	(0.0%)	13	(15.3%)	32	(37.6%)
anaemia	0	(0.0%)	1	(1.2%)	26	(30.6%)	3	(3.5%)
leukopenia	0	(0.0%)	0	(0.0%)	12	(14.1%)	14	(16.5%)
lymphopenia	0	(0.0%)	0	(0.0%)	5	(5.9%)	18	(21.2%)
febrile neutropenia	0	(0.0%)	0	(0.0%)	8	(9.4%)	3	(3.5%)
gastrointestinal disorders	**0**	**(0.0%)**	**1**	**(1.2%)**	**8**	**(9.4%)**	**1**	**(1.2%)**
nausea/vomiting	0	(0.0%)	1	(1.2%)	3	(3.5%)	0	(0.0%)
colitis/diarrhoea	0	(0.0%)	0	(0.0%)	3	(3.5%)	0	(0.0%)
abdominal pain upper	0	(0.0%)	0	(0.0%)	1	(1.2%)	0	(0.0%)
gastric ulcer perforation	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(1.2%)
strangulated umbilical hernia	0	(0.0%)	0	(0.0%)	1	(1.2%)	0	(0.0%)
infections and infestations	**0**	**(0.0%)**	**0**	**(0.0%)**	**6**	**(7.1%)**	**2**	**(2.4%)**
device related infection	0	(0.0%)	0	(0.0%)	2	(2.4%)	0	(0.0%)
colonic abscess	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(1.2%)
lung infection	0	(0.0%)	0	(0.0%)	1	(1.2%)	0	(0.0%)
peritonitis	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(1.2%)
pseudomonas infection	0	(0.0%)	0	(0.0%)	1	(1.2%)	0	(0.0%)
sepsis	0	(0.0%)	0	(0.0%)	1	(1.2%)	0	(0.0%)
sinusitis	0	(0.0%)	0	(0.0%)	1	(1.2%)	0	(0.0%)
tuberculosis	0	(0.0%)	0	(0.0%)	1	(1.2%)	0	(0.0%)
metabolism and nutrition disorders	**0**	**(0.0%)**	**0**	**(0.0%)**	**7**	**(8.2%)**	**1**	**(1.2%)**
tumour lysis syndrome	0	(0.0%)	0	(0.0%)	3	(3.5%)	0	(0.0%)
hyperglycaemia	0	(0.0%)	0	(0.0%)	2	(2.4%)	0	(0.0%)
hyponatraemia	0	(0.0%)	0	(0.0%)	1	(1.2%)	1	(1.2%)
dehydration	0	(0.0%)	0	(0.0%)	1	(1.2%)	0	(0.0%)
general disorders and administration site conditions	**1**	**(1.2%)**	**2**	**(2.4%)**	**3**	**(3.5%)**	**0**	**(0.0%)**
pyrexia	1	(1.2%)	2	(2.4%)	2	(2.4%)	0	(0.0%)
fatigue	0	(0.0%)	0	(0.0%)	1	(1.2%)	0	(0.0%)
injury, poisoning and procedural complications	**0**	**(0.0%)**	**0**	**(0.0%)**	**2**	**(2.4%)**	**2**	**(2.4%)**
infusion related reaction	0	(0.0%)	0	(0.0%)	2	(2.4%)	2	(2.4%)
nervous system disorders	**0**	**(0.0%)**	**1**	**(1.2%)**	**3**	**(3.5%)**	**0**	**(0.0%)**
headache	0	(0.0%)	0	(0.0%)	1	(1.2%)	0	(0.0%)
monoplegia	0	(0.0%)	1	(1.2%)	0	(0.0%)	0	(0.0%)
presyncope	0	(0.0%)	0	(0.0%)	1	(1.2%)	0	(0.0%)
syncope	0	(0.0%)	0	(0.0%)	1	(1.2%)	0	(0.0%)
respiratory, thoracic and mediastinal disorders	**0**	**(0.0%)**	**0**	**(0.0%)**	**3**	**(3.5%)**	**1**	**(1.2%)**
pleural effusion	0	(0.0%)	0	(0.0%)	2	(2.4%)	0	(0.0%)
acute respiratory distress syndrome	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(1.2%)
pulmonary embolism	0	(0.0%)	0	(0.0%)	1	(1.2%)	0	(0.0%)
hepatobiliary disorders	**0**	**(0.0%)**	**0**	**(0.0%)**	**3**	**(3.5%)**	**0**	**(0.0%)**
cholestasis	0	(0.0%)	0	(0.0%)	2	(2.4%)	0	(0.0%)
hepatocellular injury	0	(0.0%)	0	(0.0%)	2	(2.4%)	0	(0.0%)
investigations	**0**	**(0.0%)**	**0**	**(0.0%)**	**3**	**(3.5%)**	**0**	**(0.0%)**
aspartate aminotransferase	0	(0.0%)	0	(0.0%)	1	(1.2%)	0	(0.0%)

System Organ Class Preferred Term	Safety Set n=85							
	Grade 1 n=3		Grade 2 n=6		Grade 3 n=57		Grade 4 n=62	
creatinine renal clearance decreased	0	(0.0%)	0	(0.0%)	1	(1.2%)	0	(0.0%)
weight decreased	0	(0.0%)	0	(0.0%)	1	(1.2%)	0	(0.0%)
renal and urinary disorders	**2**	**(2.4%)**	**0**	**(0.0%)**	**0**	**(0.0%)**	**0**	**(0.0%)**
renal failure	1	(1.2%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
acute kidney injury	1	(1.2%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0**	**(0.0%)**	**1**	**(1.2%)**	**1**	**(1.2%)**	**0**	**(0.0%)**
basal cell carcinoma	0	(0.0%)	1	(1.2%)	0	(0.0%)	0	(0.0%)
tonsil cancer	0	(0.0%)	0	(0.0%)	1	(1.2%)	0	(0.0%)
psychiatric disorders	**0**	**(0.0%)**	**0**	**(0.0%)**	**1**	**(1.2%)**	**0**	**(0.0%)**
confusional state	0	(0.0%)	0	(0.0%)	1	(1.2%)	0	(0.0%)
cardiac disorders	**0**	**(0.0%)**	**0**	**(0.0%)**	**1**	**(1.2%)**	**0**	**(0.0%)**
acute coronary syndrome	0	(0.0%)	0	(0.0%)	1	(1.2%)	0	(0.0%)
immune system disorders	**0**	**(0.0%)**	**0**	**(0.0%)**	**1**	**(1.2%)**	**0**	**(0.0%)**
hypersensitivity	0	(0.0%)	0	(0.0%)	1	(1.2%)	0	(0.0%)
vascular disorders	**0**	**(0.0%)**	**0**	**(0.0%)**	**1**	**(1.2%)**	**0**	**(0.0%)**
lymphoedema	0	(0.0%)	0	(0.0%)	1	(1.2%)	0	(0.0%)

No Grade 5 has been reported during induction. According to protocol, only grade 1 and 2 SAEs were reported.