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Long-Term Follow-Up of Rituximab Maintenance in Young Patients With Mantle-Cell Lymphoma Included in the LYMA Trial: A LYSA Study

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Abstract

Clinical trials frequently include multiple end points that mature at different times. The initial report, typically based on the primary end point, may be published when key planned coprimary or secondary analyses are not yet available. Clinical trial updates provide an opportunity to disseminate additional results from studies, published in JCO or elsewhere, for which the primary end point has already been reported.

The LYMA trial demonstrated the benefit of rituximab maintenance (RM) in first-line young patients with mantle-cell lymphoma. In this prolonged follow-up of 7.5 years (95% CI, 7.4 to 7.7) from inclusion, the median progression-free survival (PFS) and overall survival (OS) for the full population were not reached (NR) with a 7-year PFS of 55.5% (95% CI, 49.5 to 61) and OS of 69.5% (95% CI, 63.8 to 74.5). The EFS remained statistically superior in favor of RM (median NR *v* 5.8 years, $P < .0001$; HR, 0.39 [95% CI, 0.52 to 0.6] and 7-year estimate, 76.2% versus 46% for RM and observation, respectively). Similarly, RM prolonged PFS (estimated PFS at 7 years, 78.5% *v* 47.4% and HR, 0.36 [95% CI, 0.23 to 0.56] for RM and observation, respectively, $P < .0001$). The 7-year OS estimate was 83.2% versus 72.2%, respectively ($P = .088$, HR, 0.63 [95% CI, 0.37 to 1.08]). Cause of death was not significantly distinct between the two groups, with lymphoma being the leading cause with a very low rate of infection-related death. Overall, the PFS benefit of RM after autologous stem cell transplantation remains after 7-year follow-up, and RM was not associated with an increase in infection-related mortality, making this

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Introduction

In mantle-cell lymphoma (MCL), recent progresses in the standard of care (SOC) led to improved overall survival (OS), but with no plateau on survival curves.[1-5] LYMA trial investigated the benefit of rituximab maintenance (RM; ClinicalTrials.gov identifier: NCT00921414) in patients with newly diagnosed MCL in response after an induction (rituximab, dexamethasone, high-dose cytarabine, platinum [R-DHAP], followed by consolidation and autologous stem cell transplantation [ASCT]) and randomly assigned to receive 3 years of RM or observation. The primary end point was met with a 4-year event-free survival (EFS) of 79% in the RM versus 61% in the observation arm. More strikingly, RM led to a significant improvement in OS (89% versus 80% for 4 years, $P = .04$) and consequently became the SOC in the MCL field.[6] Reported here are long-term safety and efficacy results, as well as postrelapse outcome.

Methods

Eligibility criteria have been previously described.[6] Between September 2008 and August 2012, 299 patients at diagnosis were enrolled (Table 1), of whom 279 received four full courses of R-DHAP and 257 in response underwent consolidation with rituximab, carmustine, etoposide, cytarabine, and melphalan regimen, followed by ASCT. Up to 3 months after ASCT (Data Supplement, Fig S1, flow chart [online only]), 240 patients were randomly assigned either to RM for 3 years (every 2 months) or observation arm, with 120 patients in each. Primary end point, EFS (defined as absence of disease progression/relapse/death, severe infection, or allergy to R), and secondary end point, PFS/OS, were previously reported with a median follow-up of 50 months.[6]

Table 1. Patients Characteristics at Random Assignment

Characteristic	Treatment Arm		ITT Set (N = 240)
	Observation (n = 120)	Rituximab (n = 120)	
Sex, No. (%)			

High-Dose Cytarabine and Autologous Stem-Cell Transplantation in Mantle Cell Lymphoma: Long-Term Follow-Up of the Randomized Mantle Cell Lymphoma Younger Trial of the European Mantle Cell Lymphoma Network

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ITT, intention to treat; LDH, lactate dehydrogenase; MIPI, Mantle Cell Lymphoma International Prognostic Index.

This unblinded, randomized prospective trial was performed according to the principles of the Declaration of Helsinki and was approved by an ethics committee. The investigators obtained informed consent from each participant or each participant's guardian.

Time-to-event survival curves were estimated with the use of the Kaplan-Meier method. Time-to-event end points in the different groups were compared with the use of log-rank tests and Cox proportional hazards regression.

We report here an overrunning analysis of the primary and secondary end points and exploratory analysis (response to postrelapse salvage strategy, time from relapse to death [OS-2], and causes of death). Post hoc exploratory analysis on survival from a risk-defining event (Landmark approach) according to progression of disease or death due to lymphoma within 2 years of first-line therapy (POD24) was performed.

Results

For this analysis, data cutoff was April 15, 2019, with a median follow-up from random assignment of 7 years (95% CI, 6.8 to 7.2) for the living patients.

Patients received a mean of 14.5 cycles of RM of the 18 expected (mean maintenance duration, 29 months). Thirty-seven of 120 patients prematurely stopped RM before the planned 3 years (30.8%, Data Supplement, Fig S1 and Table S1) including 15 because of RM toxicity and 10 to progression.

In the RM arm, 21 patients experienced a relapse versus 53 in the observation arm (Data Supplement, Table S2). Most patients received a salvage treatment (94% in the observation and 100% in the RM arm, Data Supplement, Table S3). This mainly included immunochemotherapy-based regimen in 87.5% and a targeted therapy (40%) without significant distinction between the two arms. Patients in the observation arm had a higher overall response rate and complete response to salvage compared with patients in the RM arm (Data Supplement, Table S4).

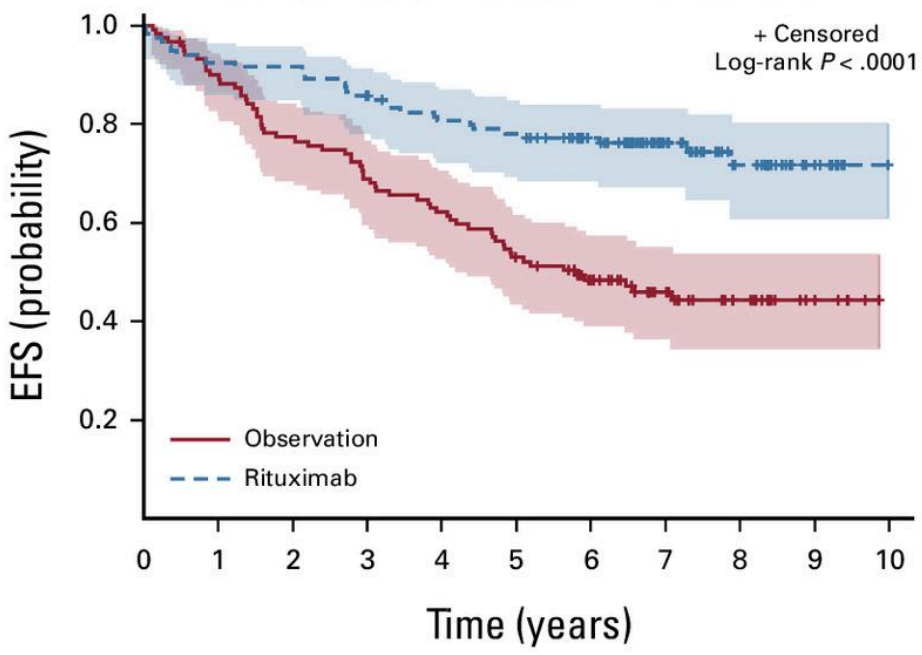
With regards to outcome analysis with this prolonged follow-up (FU), the median EFS was not reached in the RM arm versus 5.8 years, $P < .0001$ in the observation arm (Fig 1A and Data Supplement, Table S5). The estimated 7-year EFS was 76.2% (95% CI, 67.4 to 82.9) versus 46% (95% CI, 36.6 to 54.9) for RM and observation arm, respectively (HR, 0.39 [95% CI, 0.52 to 0.61). The median PFS was not reached in RM versus 6.1 years in

69.9 to 85.0) versus 47.4% (95% CI, 37.9 to 56.3) for RM and observation arm, respectively, *P* < .0001, HR 0.36 (95% CI, 0.23 to 0.56). Within the RM arm, 7 the 21 relapses post-random assignment occurred after the end of the planned 3 years of RM, and the majority (14/21, 67%) occurred within 3 years post-random assignment, suggesting that there is no increase in the incidence of relapse after the end of RM (Data Supplement, Fig S2).

A

EFS From Random Assignment According to Treatment Arm–ITT set

With No. of Patients at Risk and 95% Confidence Limits

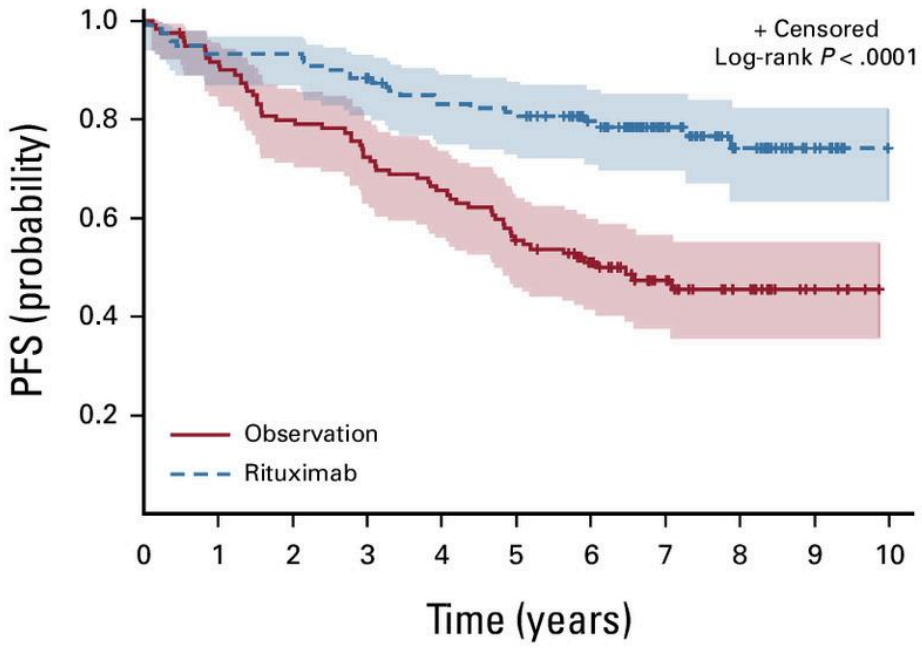


No. at risk:											
Observation	120	107	92	82	74	62	47	29	16	6	0
Rituximab	120	111	110	102	94	91	74	44	26	11	0

B

PFS From Random Assignment According to Treatment Arm–ITT set

With No. of Patients at Risk and 95% Confidence Limits

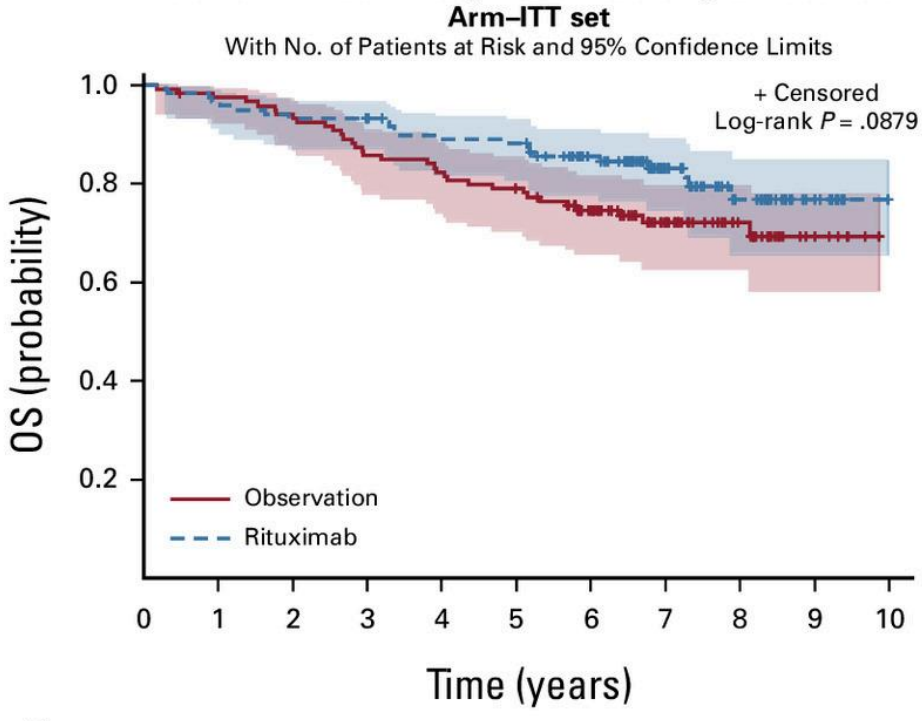


No. at risk:											
Observation	120	109	95	86	78	65	50	29	16	6	0
Rituximab	120	112	112	105	97	95	76	46	27	11	0

C

OS From Random Assignment According to Treatment Arm–ITT set

With No. of Patients at Risk and 95% Confidence Limits



No. at risk:											
Observation	120	116	112	102	98	93	75	45	25	7	0
Rituximab	120	116	112	111	104	103	81	48	28	11	0

Fig 1. Outcome by random assignment arm. (A) EFS from random assignment in the rituximab versus observation arm. (B) PFS from random assignment in the rituximab versus observation arm. (C) OS from random assignment in the rituximab versus observation arm. EFS, event-free survival; ITT, intention to treat; OS, overall survival; PFS, progression-free survival.

Median OS was not reached in both arms (Fig 1C, 7-year OS estimate, 83.2% [95% CI, 74.7 to 89.0] and 72.2% [95% CI, 62.9 to 79.5] in RM and observation arm, respectively; *P* = .088, HR, 0.63 [95% CI, 0.37 to 1.08]). Overall, since inclusion, 97 patients had died (32%), of whom 42 before random assignment and 55 after: 33 (27.5%) in the observation arm and 22 (18.3%) in the RM. No distinction in the cause of death between RM and observation arm was noticed (Data Supplement, Table S6) with a low rate of infection-related death. Of note, in a subgroup analysis, patients treated before ASCT with oxaliplatin (n = 38, see Tessoulin et al[7]) during induction had prolonged PFS and OS (Data Supplement, Figs S3A and S3B) than those treated with cisplatin or carboplatin (n = 260).

Postrelapse, patients in the RM arm presented a shorter OS-2 as compared with patients in the observation arm: with a median OS-2 of 1.1 years (95% CI, 0.7 to 2.1) versus 4.6 years (95% CI, 2 to NA) for patients relapsing in the RM and observation arm, respectively (Fig 2), without significant impact of salvage type (Data Supplement, Fig S4). In the full population from inclusion (N = 299 patients), 283 had data available for POD24[8] analysis and 47 presented a POD24 event associated with a very short postevent OS (median 0.7 year; Data Supplement, Fig S5A). POD24 patients presented at baseline with higher lactate dehydrogenase value, more frequently B symptoms, higher Mantle Cell Lymphoma International Prognostic Index (MIPI) score, more blastoid variant, and ki67 >30% than patients without POD24 event (Data Supplement, Table S7). In a multivariable model, ki67 and MIPI score appear to be prognostic factors of POD24 event (Data Supplement, Table S8). Finally, within POD24 patients, those in RM arm had a shorter OS-2, as compared with those in the observation arm (median 0.7 *v* 1.5 year in the RM versus observation arm, *P* = .01). For patients experiencing a late event (ie, relapse after 24 months), the difference was no longer significant, although RM patients tended to have a shorter OS-2 compared with observed patients (*P* = .07, median OS-2 2.1 *v* 5.2 years; Data Supplement, Figs S5B and S5C).

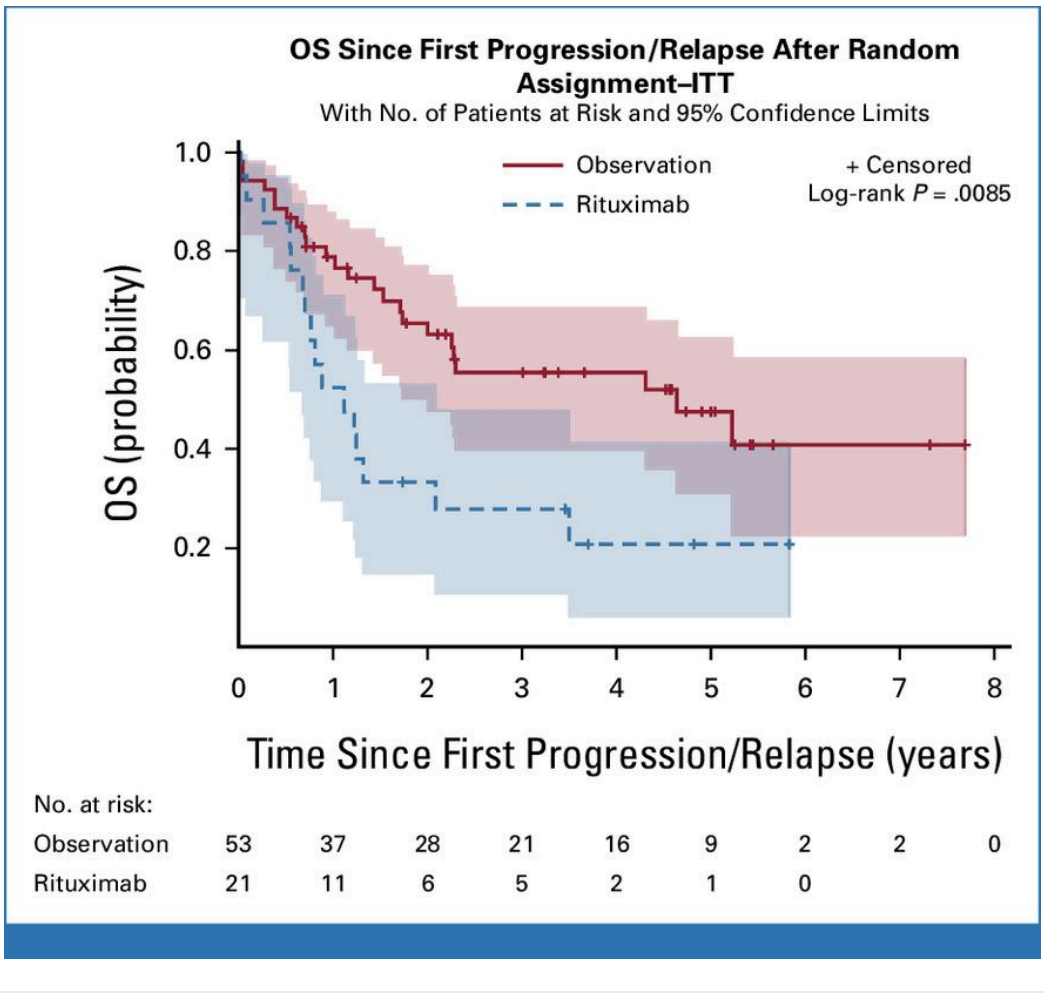


Fig 2. Postrelapse OS by random assignment arm. ITT, intention to treat; OS, overall survival.

Discussion

In this long-term FU, we demonstrated the continued efficacy and favorable safety profile of RM after ASCT for young responding patients with MCL, without increase of relapse at the end of maintenance, suggesting a long-term immunologic disease control. Furthermore, the prolonged estimated 7-year PFS for patients in the RM and observation arm (78.5% and 47.3%, respectively) suggests that MCL may be curable for a group of patients. RM significantly reduces the incidence of early and late relapses; however, as reported in other maintenance trial (PRIMA in follicular lymphoma[9]), patients who failed this optimal strategy are the one with the most aggressive disease, explaining the poor outcome postsalvage. Of note, BTKi approval in France started at end 2015, explaining the low percentage of patients who received this treatment as salvage. All in all, this long-term FU of the LYMA trial confirms that RM is safe and provides a clear benefit in outcome for patients with MCL, leading to potential cure and plateau on survival curves. Importantly, POD24 patients have a very poor outcome and represent an unmet medical need in MCL, and it seems now reasonable to design clinical trials including novel immune strategies,[10,11] on the basis of high-risk features identified as associated with this event.[12]

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Prior Presentation

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Data Sharing Statement

Baseline clinical and outcome data will be made available on request to the corresponding author S.L.G.

Authors' Disclosures of Potential Conflicts of Interest

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