Rituximab Maintenance Versus Observation After Immunochemotherapy (R-CHOP, R-MCP, and R-FCM) in Untreated Follicular Lymphoma Patients: A Randomized Trial of the Ostdeutsche Studiengruppe Hämatologie und Onkologie and the German Low-Grade Lymphoma Study Group

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Abstract

The German study groups, the German Low-Grade Lymphoma Study Group (GLSG) and Ostdeutsche Studiengruppe Hämatologie und Onkologie (OSHO), initiated in 2007 a double randomized trial to investigate efficacy and safety of rituximab maintenance versus observation in remission after randomly assigned induction treatment in the first-line follicular lymphoma. Previously untreated patients with stage II–IV follicular lymphoma in need of therapy were randomized to receive 6 cycles of R-CHOP, R-MCP, or R-FCM. Responding patients were subsequently randomized to 2 years rituximab maintenance or observation, stratified by type of immunochemotherapy, quality of remission, and Follicular Lymphoma International Prognostic Index (FLIPI). Recruitment was stopped in 2011 after the PRIMA results had been published. Median age of the 206 recruited patients was 66 years (range, 24–86), and (FLIPI) was low in 13%, intermediate in 28%, and high in 60%. High and comparable overall response rates were observed after R-CHOP (88%), R-MCP (89%), and R-FCM (91%). Rituximab maintenance substantially prolonged progression-free survival (PFS) in comparison to observation in remission (hazard ratio 0.39, $P = 0.0064$). In the rituximab maintenance group, the 3-year PFS was 89% compared with 69% in the observation group. No differences in overall survival were observed for maintenance vs. observation (hazard ratio 1.04, 95% confidence interval 0.32–3.43, $P = 0.95$). In this randomized trial, 2 years of rituximab maintenance was associated with significantly prolonged PFS in comparison to observation after response to first-line immunochemotherapy in follicular lymphoma. Our data represent an independent confirmation of the PRIMA trial results.

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Introduction

Follicular lymphoma (FL) is the most common nodal indolent lymphoma in western Europe and the United States and is incurable by chemoimmunotherapy.[1–3] The natural course of follicular lymphoma is characterized by decreasing response rates and shorter response durations with every new disease recurrence.[4,5] The addition of rituximab to first-line standard chemotherapy led not only

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to an increase in progression-free survival (PFS) but also to superior overall survival rates in most trials.[6–9] To prolong the duration of remission even further, rituximab maintenance therapy was added for patients who achieved a response after induction with either rituximab, chemotherapy, or immunochemotherapy.[10–15] A recent meta-analysis that evaluated individual patient data from 2315 patients from seven randomized controlled trials found a survival benefit for rituximab maintenance for all patients except for patients after rituximab-containing first-line therapy.[16] The latest follow-up of the pivotal PRIMA study confirmed the statistically and clinically significant improvement of the median PFS of 10.5 years in the maintenance compared to 4.1 years in the observation arm after response to immunochemotherapy.[17] But even with a mature median follow-up of 9.0 years, the PRIMA study failed to show an overall survival benefit for patients who received a 2-year rituximab maintenance therapy after induction with rituximab in combination with chemotherapy. The present double randomized GLSG-OSHO70-trial that started in 2007 was designed to first identify the optimal rituximab combination chemotherapy (R-CHOP versus R-MCP versus R-FCM) for untreated advanced stage FL patients and second to assess whether a rituximab maintenance therapy would improve PFS for patients with at least partial remission (PR) after induction. After publication of the results of the PRIMA trial[13] and approval of rituximab for maintenance therapy after first-line induction in FL patients, the second randomization between rituximab maintenance and observation was stopped in October 2011 and subsequently all patients received rituximab maintenance therapy. At the same time, recruitment to GLSG-OSHO70 was closed prematurely due to slow accrual since results of the StiL NHL1-2003-study suggested that rituximab-bendamustine was at least as efficacious and less toxic as R-CHOP.[18] Here, we present the final trial results.

Patients and methods

Trial design, patients, and treatments

The GLSG-OSHO70-study was an open-label, multicenter, factorial, randomized phase III trial in patients with previously untreated, high–tumor-burden follicular lymphoma in need of treatment. Eligibility criteria were diagnosis of a stage III or IV or stage II with bulky disease, untreated, CD-20-positive follicular lymphoma (histologic grade 1, 2, or 3a), age ≥18 years and the presence of modified GELF-criteria (B symptoms, hematopoietic insufficiency, organ compression, nodal involvement >7cm, and malignant effusion).[19] Patients had to be ineligible for myeloablative high-dose chemotherapy and autologous stem cell transplantation either due to patient's refusal or due to comorbidities or advanced age (≥65 years). Exclusion criteria included a diagnosis of FL grade 3b, evidence of histologic transformation into an aggressive lymphoma at the time of diagnosis, central nervous system involvement, or history of previous malignancy. The study comprised 2 parts: The first randomization at inclusion was 1:1:1 among 3 different induction chemoimmunotherapy regimens (R-CHOP versus R-MCP versus R-FCM, for details see Supplemental Digital Table 1, http://links.lww.com/HS/A166). Patients who achieved at least a PR at the end of induction were then randomized 1:1 between observation and rituximab maintenance. Both randomizations were blocked and stratified for Follicular Lymphoma International Prognostic Index (FLIPI) risk groups, and the second randomization was additionally stratified for type of induction treatment and response quality at the end of induction. Randomization was performed centrally by computer random number generation upon investigator request via fax. Blinding was not feasible. The primary end point for the first randomization was complete response (CR) rate (excluding CRu) after induction therapy, and the primary end point of the second randomization was PFS from end of induction. Key secondary endpoints were CR/CRu rates, failure-free survival (FFS) from first randomization to either stable disease at the end of

induction, progression or death, time from randomization to initiation of a new antilymphoma treatment (TTNT), overall survival (OS) from randomization until death from any cause, and toxicities (CTCAE V 3.0).

The GLSG-OSHO70 trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The study protocol and all amendments were approved by the ethics committee of the State Medical Board of Thuringia and the national competence authority (Paul-Ehrlich-Institute). All patients provided written informed consent.

Response was assessed according to the 1999 International Working Group criteria for non-Hodgkin lymphoma.[20] The restaging after induction therapy was performed 2–4 weeks after the last rituximab infusion of induction. Patients who achieved a CR, CRu, or PR were randomized to either observation or maintenance rituximab 375mg/m² every 8 weeks for 2 years. Rituximab maintenance started 4–8 weeks after the last rituximab administration of induction therapy. Patients in both arms had response assessment by clinical evaluation every 8 weeks and a computed tomographie (CT) scan every 6 months during observation /maintenance. Clinical examination of patients who completed 2 years of maintenance treatment or observation was scheduled every 3 months for the first year and every 6 months from then on. CT scans were performed every 6 months or when clinically indicated. Relapses or progressions were determined based on clinical or radiologic assessment.

The trial was initially planned to have 95% power to detect significant differences among the 3 induction arms in the case of true improvements in complete remission rates from 20% to 35%. Similarly, it was planned to have 95% power to detect significant differences for maintenance versus observation in the case of a true PFS hazard ratio of 0.60. Allowing for 5% dropouts during the induction period and additional 15% patients not undergoing randomization for maintenance, a total number of 878 was necessary to answer the trial questions and considered feasible to be recruited within 7 years.

The trial recruitment was closed prematurely on October 10, 2011 after the results of the PRIMA study showed a significant PFS benefit for rituximab maintenance treatment after first-line rituximab chemoimmunotherapy for advanced stage FL patients. Moreover, patient accrual had been very low after the presentation of the results of the StiL-NHL1-study at the ASH meeting in 2009,[18] so the Ostdeutsche Studiengruppe Hämatologie und Onkologie and German Low-Grade Lymphoma Study Group study groups decided to close the study recruitment without knowledge of the results for the 2 parts of the study up to that point. At recruitment stop, 206 patients had been randomized for induction therapy and 131 patients had undergone second randomization. After the termination of study enrollment, all patients who completed induction therapy and achieved at least a PR were assigned to rituximab maintenance therapy. Clinical follow-up ended on March 20, 2013.

BCL2/IgH minimal residual disease detection

BCL2/IgH minimal residual disease (MRD) assessments from peripheral blood (PB) and bone marrow (BM) samples were performed by quantitative PCR as described earlier.[21] Samples with <50,000 tested cells were regarded as noninformative. A BCL2/IgH-MRD marker was established if BCL2/IgH frequency was >1/100,000 in an initial blood or bone marrow sample or if a corresponding BCL2/IgH rearrangement could be detected in a diagnostic lymph node. Samples from patients without MRD marker were excluded from analysis.

Statistical analyses

The pairwise comparisons of CR rates between induction arms were performed by Fisher's exact test using a two-sided

significance level of 1.67% each to maintain an overall significance level of 5% (Bonferroni-correction). The primary endpoint to evaluate maintenance versus observation was monitored sequentially by means of a two-sided truncated probability ratio test (Whitehead 1992) for the log-rank statistics with an overall significance level of 5%. The sequential design allowed early stopping for superiority and futility.

The primary analysis cohorts were according to the intention-to-treat with the modification that patients in whom the diagnosis of FL grade 1–3a was not confirmed based on pretreatment histology were excluded. Furthermore, for primary analysis of the induction part, patients without any staging results during induction were excluded as dropouts and the latest staging result was used for patients without staging result at the end of induction. For primary analysis of the maintenance part, PFS was calculated in patients with at least PR from end of induction to progression or death from any cause, censored at last date in remission in patients without progression at last contact and at initiation of a new antilymphoma treatment. PFS and FFS were censored at last date without failure, TTNT at the last date without initiation of a new treatment, OS at last contact date in patients without respective events. Time-to-event endpoints were described by Kaplan–Meier estimates. In sensitivity analyses, differences for time-to-event endpoints between trial arms were adjusted for FLIPI risk groups and ECOG performance status using multiple Cox regression. To explore a potential modification of maintenance PFS effects by induction treatment, an interaction analysis was performed by means of multiple Cox regression. For safety analyses, patients were evaluated according to the treatment strategy actually started.

MRD negativity rates at the end of induction in PB, BM, and pooled PB/BM were compared between treatment groups by exact tests. In the pooled PB/BM evaluation, a patient was considered MRD positive if at least one available PB or BM sample was MRD positive; a patient was considered MRD negative only if all other available samples for the same time point were MRD negative. As sensitivity analyses, samples within a 3-month window after the EOI staging time point were included in the evaluation, considering a patient MRD positive if at least 1 positive MRD sample was observed during this time period. P values for comparisons of secondary endpoints were interpreted as hypothesis generating.

Results

Induction therapy

The median age of the 206 patients who underwent the first randomization between June 6, 2007, and July 28, 2011, was 66 years, and the age as well as FLIPI risk were well balanced among the 3 treatment groups (Supplemental Digital Table 2, http://links.lww.com/HS/A166). For the analysis of the primary end point of the first randomization, the CR rate of the induction therapy regimens of 190 patients were evaluable (Supplemental Digital Figure 1, http://links.lww.com/HS/A166). After induction with R-FCM, 25/58 patients (43%) achieved a CR compared to 23% (15/66 patients) and 24% (16/66 patients) for R-CHOP and R-MCP, respectively (Supplemental Digital Table 3, http://links.lww.com/HS/A166). Pairwise comparisons showed no statistically significant difference in CR rates between treatment arms at the 1.6667% significance level (correction for multiple testing). Of note, due to the reduced sample size, a statistical power of only about 30% can be assumed to detect the initially planned clinically relevant differences. Similarly, overall response rates were not different between induction therapy arms (88% versus 91% versus 89% for R-CHOP, R-FCM, and R-MCP, respectively; Supplemental Digital Table 3, http://links.lww.com/HS/A166).

After a median follow-up of 3.5 years, there was no clear difference in FFS between the three treatment arms ($P = 0.086$). The

estimated 3-years FFS rate was 62% (95% confidence interval [CI] 48%–73%) in the R-CHOP-arm, 86% (95% CI 73%–93%) after R-FCM, and 71% (95% CI 58%–81%) in the R-MCP-arm (Figure 1A). After adjustment for differences in ECOG and FLIPI, the FFS hazard ratio was 0.44 (95% CI 0.22–0.89, $P = 0.023$) for R-FCM versus R-CHOP and 0.87 (95% CI 0.49–1.55, $P = 0.64$) for R-MCP versus R-CHOP. There were no differences in overall survival between patients treated with R-CHOP, R-FCM, or R-MCP chemoimmunotherapy ($P = 0.60$, Figure 1B).

Rituximab maintenance therapy

Out of 206 patients randomized for induction, 131 patients underwent the second randomization. Main reasons for not being randomized between maintenance and observation were premature discontinuation of induction (24 patients, R-FCM: 16), no response to induction (18 patients), delay of induction (9 patients), and assignment to rituximab maintenance after stop of randomization (12 patients, Figure 2). After exclusion of 3 patients because of FL 3b histology, 63 and 65 patients in the observation and in the rituximab maintenance arm were evaluable for PFS, the primary endpoint of the second randomization (Figure 2). Patients in the maintenance arm had a significantly
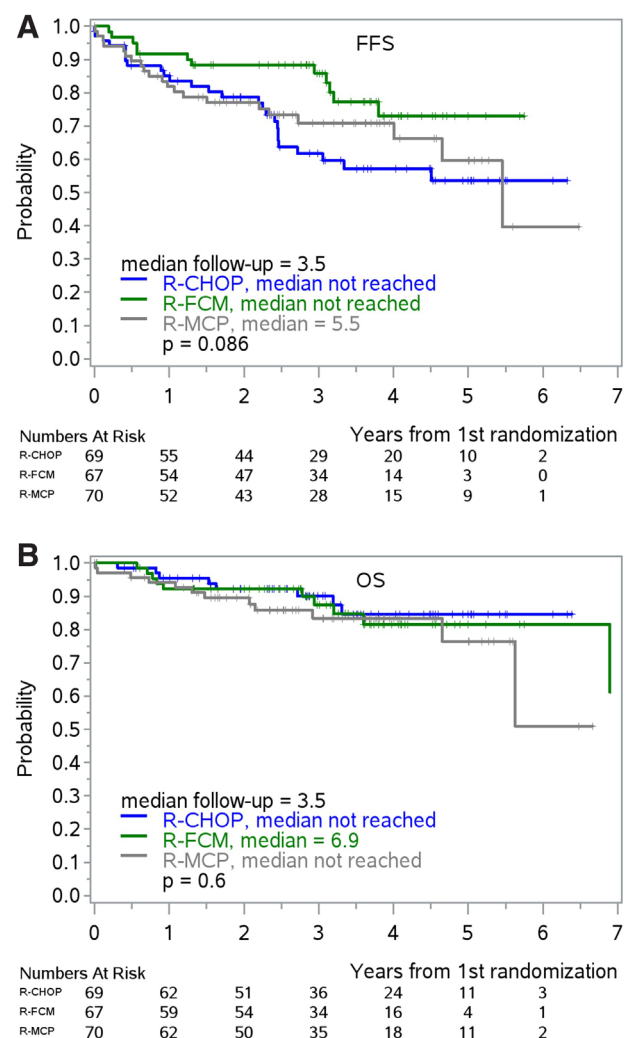

Figure 1. Treatment outcome after immunochemotherapy with R-CHOP, R-FCM or R-MCP for untreated FL patients. Failure-free survival (FFS, A) and overall survival (OS, B) according to induction therapy regimen.
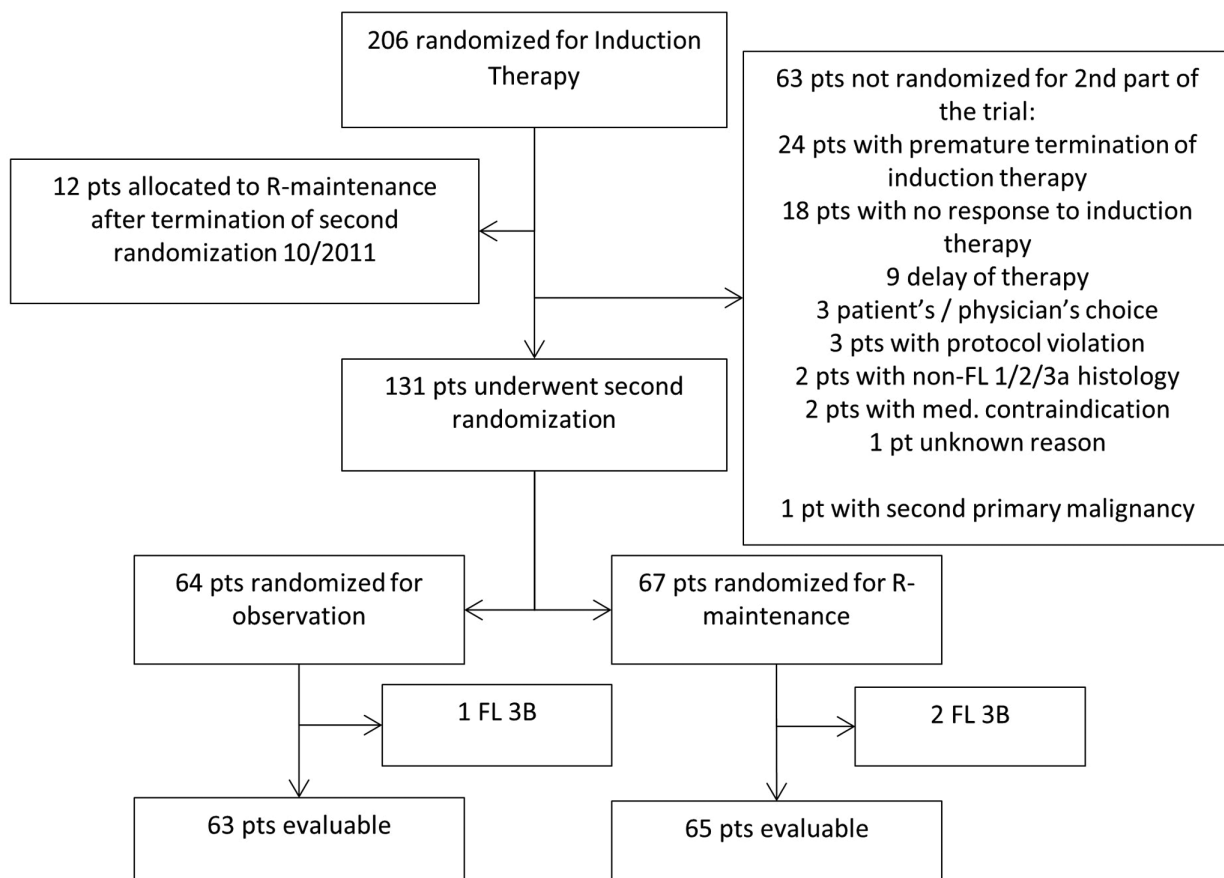
Figure 2. CONSORT diagram for patient allocation at second randomization. FL = follicular lymphoma; R = rituximab.

prolonged PFS compared to patients in the observation arm (hazard ratio 0.39, P = 0.0064 after the correction for interim analyses, Figure 3A). Secondary Cox-regression analyses showed a hazard ratio of 0.31 (95% CI 0.14–0.71, P = 0.006) for R-maintenance with similar results after adjustment for FLIPI (0.30, 95% CI 0.13–0.70, P = 0.005), ECOG performance status, or type of induction therapy. After a median follow-up of 3.2 years, the estimated 3-year PFS of responding patients was 69% (95% CI 54%–80%) for the observation and 89% (95% CI 78%–95%) for the rituximab maintenance arm. The P value for the interaction term between the treatment arms of the first and the second part of the study was 0.53; hence, there was no indication that the effect of the rituximab maintenance therapy on PFS was influenced by the type of induction therapy.

Similar to the effects on PFS, patients in the R-maintenance treatment arm had prolonged time to next treatment (TTNT) compared to patients in the observation arm (P = 0.0089, estimated 3-year TTNT rate 89% [95% CI 76%–95%] and 71% [95% CI 57%–82%] for R-maintenance versus observation, Figure 3B, HR 0.32, 95% CI 0.13–0.79). A total of 17 patients received second-line lymphoma treatment, 14 patients in observation and 3 patients in the R-maintenance arm. Seven patients died without the start of a second-line treatment, 3 patients in the observation, and 4 patients in the maintenance arm.

There was no difference in overall survival between the 2 treatment arms (Figure 3C). After a median follow-up of 3.2 years, 6 of 67 patients in the R-maintenance and 5 of 64 patients in the observation arm had died, resulting in a Hazard-ratio of 1.04 (95% CI 0.32–3.43, P = 0.95), with similar results after adjustment for FLIPI (1.07, 95% CI 0.32–3.51, P = 0.92), ECOG performance status, and induction therapy. The estimated 3-year

OS rates were 91% (95% CI 78%–96%) for the R-maintenance arm and 92% (95% CI 80%–97%) in the observation arm of the study.

Toxicity

During induction, therapy marked differences in toxicity were only observed for hematological toxicity and polyneuropathy. Patients treated with R-FCM and R-MCP had higher rates of grade 3–4 leukopenia (92% and 88%) compared to R-CHOP patients (63%). Similarly, R-FCM caused the highest rates of thrombocytopenia (70%, grade 3–4: 17%; R-MCP 49%, grade 3–4: 6%; R-CHOP 25%, grade 3–4: 3%). Despite these differences in hematotoxicity, there was no clear difference in the rates of febrile neutropenia or infections with or without neutropenia among the 3 immunochemotherapy regimens. As expected, neurological toxicity was most pronounced in the R-CHOP treatment arm (40%, grade 3–4: 6%) compared to R-FCM (16%, grade 3–4: 3%) and R-MCP (14%; grade 3–4: 1%).

Seventy-nine patients started rituximab maintenance therapy, 66 patients who were randomly assigned, and 12 patients who were allocated to maintenance therapy after randomization were stopped. One patient who received rituximab maintenance had not undergone second randomization and terminated rituximab maintenance prematurely. Another patient who was randomized to rituximab maintenance withdrew consent and did not receive maintenance therapy. The median duration for 78 patients with documentation of the maintenance treatment was 20 months (0–23 months).

Sixty-nine patients out of 78 patients (88%) who started rituximab maintenance completed 2 years of maintenance treatment.
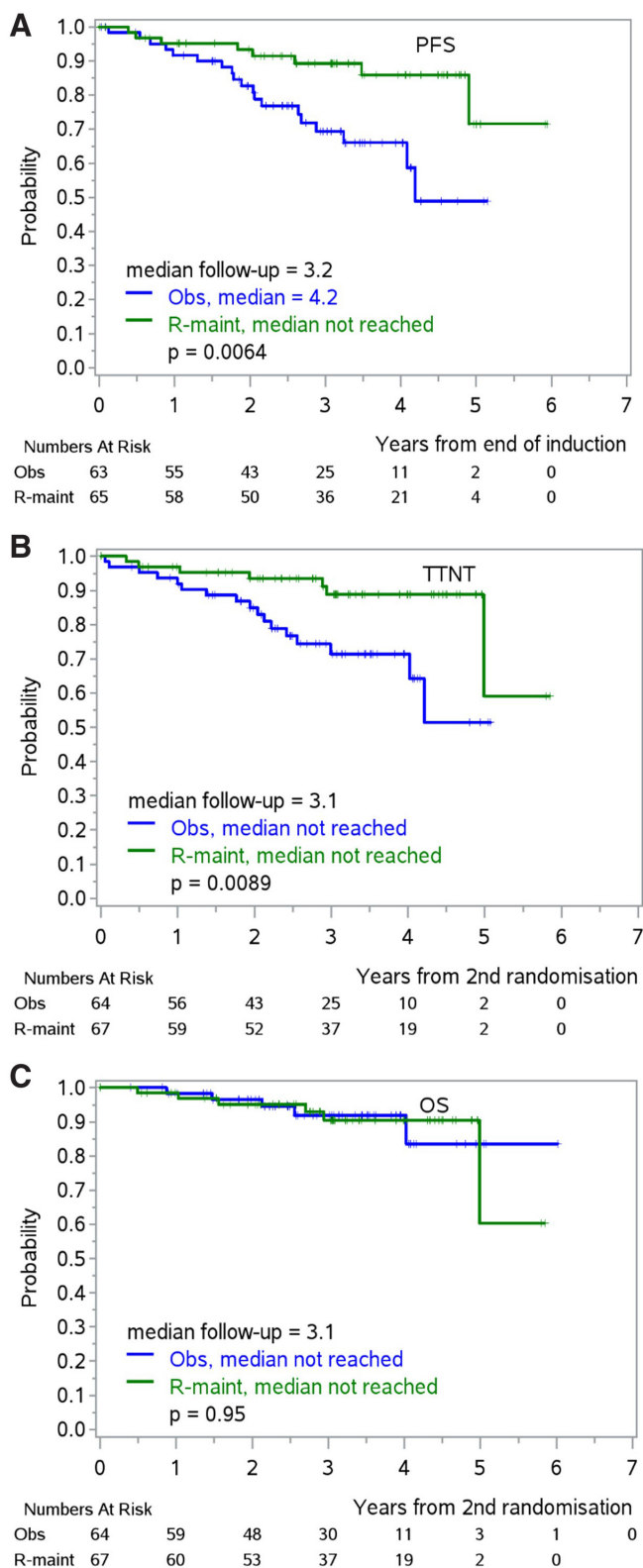
Figure 3. Treatment outcome after rituximab maintenance therapy versus observation for patients in remission after induction immunochemotherapy. Progression-free survival (PFS, A), time to next therapy (TTNT, B), and OS (C) for evaluable (PFS) and all patients (TTNT and OS) who underwent 2 randomizations.

Reasons for maintenance discontinuation were toxicity in 3, patient's or physician's decision in 3, and unknown reasons in 3 patients. In general, rituximab maintenance therapy was well

tolerated and there were only a very few toxicities of grade 3 or 4 (Supplemental Digital Table 4, http://links.lww.com/HS/A166). There was a trend for an increased rate of leukopenia (grade 1–5 leukopenia: R-maintenance 58% versus observation 40%, $P = 0.067$; grade 3 or 4 leukopenia: R-maintenance 16% versus observation 7%), and the higher rate of leukopenia was statistically significant in the subgroup of patients ≥65 years (grade 1–5 leukopenia: R-maintenance 67% versus observation 37%, $P = 0.02$; grade 3 or 4 leukopenia: R-maintenance 19% versus observation 6 %, Supplemental Digital Table 5, http://links.lww. com/HS/A166). But the higher leukopenia rate in the rituximab maintenance arm did not transform into clear differences in neutropenia, febrile neutropenia, or infections with or without neutropenia (Supplemental Digital Table 4, http://links.lww.com/ HS/A166). There was also a trend for a higher rate of gastrointestinal (GI) toxicity, which was predominantly grade 1 and 2 (grade 1–5 GI toxicity: R-maintenance 26% versus observation 10%, $P = 0.040$). Four patients in the observation arm had grade 3/4 cardiac events compared to no grade 3 or 4 cardiac events in the R-maintenance arm ($P = 0.038$, Supplemental Digital Table 4, http://links.lww.com/HS/A166). Except for the slightly higher rate of leukopenia rituximab maintenance showed no increased toxicity in elderly patients (≥65 years of age, Supplemental Digital Table 5, http://links.lww.com/HS/A166).

A total of 30 patients have died, of these 8, 9, and 13 patients were treated with R-CHOP, R-FCM, and R-MCP, respectively. Six patients have died after R-maintenance treatment, all 6 patients died >45 days after the completion of maintenance therapy. The most common causes of death were lymphoma progression (19 patients).

Minimal residual disease

For 19 out of 206 patients who underwent the first randomization, no samples for MRD marker establishment were submitted. In the remaining 187 patients, we were able to establish a BCL2/IgH-MRD marker for 89 patients (48%) from PB, BM, or diagnostic lymph node samples. Patients with BCL2/IgH-MRD marker were slightly younger (median age 64 versus 67 years, $P = 0.027$) and had a slightly lower FLIPI risk score (Supplemental Digital Table 6, http://links.lww.com/HS/A166). Fifty-four patients had an MRD sample at the end of induction immunochemotherapy, all of which had achieved a clinical response. The BCL2/IgH MRD negativity rate was slightly higher after R-FCM compared to R-CHOP (93% of 14 versus 83% of 18, Table 2), with lowest MRD negativity rates after R-MCP induction treatment (77% of 22, $P = 0.53$). We obtained similar results if MRD samples that were tested within 3 months after the end of induction were included (n = 65, Table 2). For conclusions about the prognostic implications of MRD results or the differential effectivity of rituximab maintenance therapy, the number of BCL2/IgH-MRD samples was too small.

Discussion

One of the aims of this study was to identify the most efficacious induction treatment for patients with untreated follicular lymphoma in need of therapy. Unfortunately, the primary end point of the first randomization of this study, the CR rate after induction therapy with either R-CHOP, R-MCP, or R-FCM showed no significant difference among the 3 treatment arms. Similarly, FFS as well as OS at 3 years were not different between treatment arms. One reason for this negative result of the first randomization is the substantially reduced statistical power due to the premature termination of the study recruitment. We therefore can by no means conclude from our data that the 3 induction arms are equally effective. The toxicity profile of the 3 induction therapy regimens was as expected

Table 1.

Baseline Characteristics of Evaluable Patients who Underwent Second Randomization

		Observation			R-Maintenance			
Variable	Value	n	Number of Patients/Median (Min-Max)	%	n	Number of Patients/Median (Min-Max)	%	*P*
Age at randomization	≥65 y	63	36	57	65	38	58	>0.99
Sex	Male	63	31	49	65	28	43	0.59
ECOG	0	63	26	41	65	27	42	0.80
	1		35	56		34	52	
	2		2	3		4	6	
	3		0	0		0	0	
Histological diagnosis	FL Grade 1/2	63	54	86	65	54	83	0.58
	FL Grade 3A		7	11		6	9	
	FL NOS		2	3		5	8	
Stage	II	31	2	6	26	3	12	0.38
(Ann Arbor)	III		15	48		8	31	
	IV		14	45		15	58	
B-symptoms	Present	63	19	30	65	25	38	0.36
Bone marrow involvement	Present	31	8	26	26	14	54	0.055
Hemoglobin	<12 g/dl	63	14	22	63	10	16	0.50
LDH	>ULN	63	28	44	65	14	22	0.008
Number of nodal sites	>4	62	19	31	65	25	38	0.46
FLIPI	Low risk	63	6	10	65	11	17	0.52
	Intermediate risk		19	30		18	28	
	High risk		38	60		36	55	
Induction immunochemotherapy	R-CHOP	63	26	41	65	22	34	0.70
	R-FCM		15	24		19	29	
	R-MCP		22	35		24	37	
Response after induction	CR	63	17	27	65	26	40	0.29
	CRu		24	38		19	29	
	PR		22	35		20	31	
Median age at randomization	(years)	64	65 (33–76)		67	65 (25–86)		0.87
Median LDH/ULN		64	0.96 (0.53–2.4)		67	0.81 (0.55–3.3)		0.067
Median hemoglobin	(g/dl)	64	13.7 (7.1–16.6)		67	13.8 (8.9–16.8)		0.93

ECOG = ECOG Performance Status; FL = follicular lymphoma; FLIPI = Follicular Lymphoma International Prognostic Index; LDH = lactate-dehydrogenase; n = number of patients with nonmissing value; NOS = not otherwise specified; *P* = P value for exact Fisher-Test or exact Test according to Mehta and Patel[37] or Mann–Whitney U test; PR = partial remission; ULN = upper limit of normal.

Table 2.

BCL2/IgH MRD Results at End of Induction According to Immunochemotherapy Regimen

	R-CHOP			R-FCM			R-MCP			
BCL2/IgH MRD-Negativity at EOI	n	Number of Patients		n	Number of Patients		n	Number of Patients		*P*[a]
PB	18	16	89%	14	14	100%	22	18	82%	0.26
BM	8	6	75%	6	5	83%	5	3	60%	0.82
PB+BM combined	18	15	83%	14	13	93%	22	17	77%	0.53
PB (Q1 included)	21	19	90%	18	17	94%	26	22	85%	0.70
BM (Q1 included)	9	7	78%	6	5	83%	6	4	67%	>0.99
PB+BM combined (Q1 included)	21	18	86%	18	16	89%	26	21	81%	0.83

Q1 included: includes results from patients without EOI MRD sample who had a MRD sample within 3 months after EOI.
[a]Exact test according to Mehta and Patel.[37]
BM = bone marrow; EOI = end of induction immunochemotherapy; PB = peripheral blood.

with the highest rates of hematotoxicity after R-FCM and lowest rates after R-CHOP. However, the significant differences in hematotoxicity did not translate into clear differences in rates of infectious complications. Regarding neurologic adverse events, we observed the expected rates of increased vincristine-associated polyneuropathy after R-CHOP compared to F-MCP and R-FCM. The FOLL05 trial of the Fondazione Italiana Linfomi compared R-CVP, R-FM, and R-CHOP as induction treatment for patients with advanced follicular lymphoma and reported comparable results: the fludarabine-containing regimen R-FM caused higher rates of grade 3 and 4 hematotoxicity than R-CHOP and R-CVP but had similar PFS as the other anthracycline-containing regimen R-CHOP, with no difference in OS among the 3 treatment arms.[22,23] Rummel et al[18,24] conducted a noninferiority trial in patients with untreated indolent NHL that also including patients with mantle cell lymphoma. This StiL1-trial reported that R-bendamustine (BR) was at least as efficacious as R-CHOP regarding overall response and CR rate as well as PFS but was significantly less toxic than R-CHOP. These results were confirmed by the BRIGHT study, comparing R-bendamustine to R-CHOP and R-CVP,[25,26] which led to the implementation of BR as standard first-line treatment of

advanced FL in addition to established regimens like R-CHOP and R-CVP.[27,28]

Although the 3.2-year median follow-up of the present study is short for follicular lymphoma, the results of the second randomization confirm the results of the PRIMA study.[13,17] The 2-year rituximab maintenance treatment led to a statistically significant and clinically meaningful longer PFS (hazard ratio 0.39, P = 0.0064) and an increased TTNT compared to observation. With limited statistical power, we could not detect differences in OS. Similar to the results of the PRIMA study, patients benefited from rituximab maintenance treatment irrespective of the type of induction chemoimmunotherapy. The toxicity of rituximab maintenance treatment was comparable to that in the observation arm except for slightly higher rates of leukopenia and more gastrointestinal toxicity. Bachy et al[17] reported a higher number of deaths due to infections in the maintenance arm, potentially due to much smaller patient numbers and shorter follow-up, there was no difference in deaths due to infections in our study. Similarly, with short follow-up, we could not confirm the higher number of deaths due to second malignancies in the observation arm of the PRIMA study. Therefore, conclusions from our study with regard to the toxicity of a 2-year rituximab maintenance therapy should be interpreted with caution. A meta-analysis of 2586 patients from 9 rituximab maintenance trials found a higher rate of grade 3 or 4 adverse events, and in particular a hazard ratio of 3.55 for grade 3 or 4 infections in patients with rituximab maintenance compared to observation.[16] This points out that rituximab maintenance, although generally well tolerated, is associated with relevant toxicity. The meta-analysis by Vidal et al[16] found, similar to our study, a significant improvement in PFS for rituximab maintenance (HR 0.54, 95% CI 0.48–0.60), which was consistent for previously untreated and relapsed patients. Even though rituximab led to an improved OS in the total cohort of 2586 patients (HR 0.76, 95% CI 0.62–0.92), a subgroup analysis showed that only patients with relapsed or refractory lymphoma had a clear benefit with rituximab maintenance (HR 0.72, 95% CI 0.57–0.91), whereas patients who received rituximab maintenance after response to first-line treatment demonstrated no clear improvement in OS (HR 0.86, 95% CI 0.60–1.25). This lack of OS benefit despite a significant improvement of PFS which was observed in this and other studies of rituximab maintenance after first-line induction therapy[16,17,29] might have several explanations. First, in FL, which has a median OS well beyond 10 years now,[3,30] trials that are powered to show the impact of first-line treatment on OS are not feasible. Second, with a long median OS and the availability of a steadily increasing number of effective salvage therapy options, PFS to the first-line treatment might not be as relevant for long-term survival as in the prerituximab era. But even with effective salvage treatment options, there are FL patients with significantly inferior outcomes, especially patients with disease progression within 2 years after first-line induction[30–32] and transformation.[30,33] To identify those FL patients for whom rituximab maintenance might not achieve long-term disease control new strategies are needed. Molecular prognosis scores like the m7-FLIPI[34] or minimal residual disease detection[21,35,36] might aid to develop treatment strategies that help to individualize therapy and identify patients who derive the greatest benefit from rituximab maintenance therapy after first-line immunochemotherapy.

Disclosures

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