

The Use and Effectiveness of Rituximab Maintenance in Patients with Follicular Lymphoma Diagnosed Between 2004 and 2007 in the United States

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BACKGROUND: The authors examined the “real-world” effectiveness of rituximab (R) maintenance therapy (R-maintenance) compared with observation after R-based induction therapy in patients with previously untreated follicular lymphoma (FL) in the United States. **METHODS:** The National LymphoCare Study is a prospective, multicenter, observational study that enrolled >2700 untreated patients with FL diagnosed from 2004 to 2007 at 265 sites in the United States. Among these, patients who achieved at least stable disease after R-based induction therapy were eligible for the current analysis. Patients who initiated R-maintenance within 215 days of completing induction therapy were categorized as the R-maintenance group, and those who did not initiate therapy during this period were categorized as the observation group. The objective of the current study was to determine the effect of R-maintenance on progression-free survival (PFS), time to next treatment (TTNT), and overall survival (OS). **RESULTS:** A total of 1439 patients completed R-based induction therapy, 1186 of whom met all inclusion criteria (541 patients received R-maintenance and 645 patients were observed). Characteristics that were found to be predictive of receiving R-maintenance were histology grade (1/2), Ann Arbor stage of disease (III/IV), geographic region (region other than the West), and practice setting (community practice). With a median follow-up of 5.7 years, R-maintenance was associated with superior PFS (hazards ratio [HR], 0.68; 95% confidence interval [95% CI], 0.56-0.84 [$P = .0003$]) and TTNT (HR, 0.66; 95% CI, 0.52-0.84 [$P = .0007$]). No significant difference in OS was observed (HR, 0.81; 95% CI, 0.58-1.14 [$P = .23$]). **CONCLUSIONS:** R-maintenance in patients with FL and at least stable disease after R-based induction therapy provided significantly longer PFS and TTNT in comparison with observation, but no significant difference in OS was observed with 5-years of follow-up. This comparative effectiveness study aligns with the results of randomized trials suggesting that similar outcomes occur with R-maintenance in FL with the treatment variations observed in clinical practice. *Cancer* 2014;120:1830-7. © 2014 The Authors. *Cancer* published by Wiley Periodicals, Inc. on behalf of *American Cancer Society*. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

KEYWORDS: follicular lymphoma, rituximab maintenance, frontline therapy, outcomes, non-Hodgkin lymphoma.

INTRODUCTION

Follicular lymphoma (FL) is the most common indolent lymphoma in the United States.^{1,2} The majority of patients with FL present with advanced disease (Ann Arbor stage III or IV) and are considered incurable with standard therapy, which has led to marked heterogeneity in goals of therapy and, consequently, practice patterns across the United States.^{3,4} In the prirituximab era, FL has been associated with a high overall response rates to initial therapy⁵ coupled with repeated recurrences and disease-free intervals that become progressively shorter.⁶ Management strategies that may extend the disease-free interval in patients with FL have been investigated, including the use of rituximab (R) maintenance therapy (R-maintenance).⁷⁻¹⁰

The randomized Primary Rituximab and Maintenance (PRIMA) study demonstrated that 2 years of R-maintenance after first-line treatment with chemoimmunotherapy in patients with FL improved progression-free survival (PFS) in comparison with observation,¹¹ leading to the approval of R-maintenance after R-based induction therapy in 2011. Before the publication of the PRIMA study results, the clinical benefit of R-maintenance was reported in randomized studies including patients with recurrent or resistant FL who were treated with chemotherapy or chemoimmunotherapy.^{8,9,12}

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In addition, R-maintenance was studied in previously untreated patients who received single-agent R induction^{7,10} or chemotherapy alone¹³ and again was found to be associated with prolonged PFS. To the best of our knowledge, no head-to-head data are available comparing the various schedules and duration of maintenance dosing. Based on these reports, R-maintenance has been used frequently in clinical practice in the United States and other countries. The objective of the current analysis of the National LymphoCare Study (NLCS) was to examine choice of schedule and duration of R-maintenance used by practicing physicians in the United States after R-containing induction therapy; delineate the clinical characteristics, treatment setting, and response to induction associated with R-maintenance; and report on the “real-world” effectiveness of R-maintenance compared with observation after R-based induction therapy in previously untreated patients with FL.

MATERIALS AND METHODS

The NLCS is a prospective, multicenter, observational study collecting data regarding > 2700 previously untreated patients with FL diagnosed from 2004 to 2007 at 265 sites in the United States, as previously described.⁴ Written informed consent was obtained from individual patients before participation and the protocol was approved by each Institutional Review Board. Eligible patients for this study were adults (age ≥ 18 years) diagnosed with FL within 6 months of enrollment, and with no prior history of lymphoma. This analysis was further restricted to patients who had at least stable disease (SD) after an R-based induction regimen. Patients with mixed or non-FL histology or those who developed disease progression before receiving treatment were excluded from analysis. There was no central pathology review; the local pathology report defined FL diagnosis after investigators were educated regarding World Health Organization classification system definitions of FL.⁴ Initial and subsequent management decisions were made by the treating physician without protocol-specified treatment assignments or recommendations. All response assessments were made by the treating physician and were reported quarterly. Safety data were limited to treatment-related toxicity as measured by death, early treatment discontinuation, and hospitalization.

NLCS data management and analysis are guided by an advisory board composed of academic investigators and a patient advocate, some of whom coauthored this article (J.W.F., B.K.L., J.R.C., and C.R.F.). The advisory board participated in all phases of the study, including initial protocol design, prospective determination of data to

be collected, and consideration of participating sites. The advisory board meets quarterly, has full access to data listings, and collaborated with the primary author (L.J.N.) and the sponsor regarding the interpretation and publication of the data. This article was written de novo by the primary author (L.J.N.) and members of the advisory board after the approval of a protocol with prespecified endpoints, hypotheses, and plans for analysis.

Patients who were on study and had not experienced progressive disease (PD) 215 days after completing initial therapy with an R-based regimen and who achieved a complete response (CR), partial response (PR), or SD were included in the current analysis. Patients were included in the following groups: observation if no additional treatment was initiated within 215 days after the completion of initial therapy or R-maintenance if R-maintenance and no additional treatment was initiated within 215 days after the completion of initial therapy. The 215-day period was chosen based on prior studies^{7,8,13} and reviewing the distribution of the number of days between the end of induction and the start of subsequent R-maintenance, but before any outcomes analyses were performed. Approximately 90% of the patients who had received R-maintenance initiated maintenance within 215 days from the end of their first treatment. Second-line treatment was defined as the second treatment management strategy assigned by the treating physician. However, if R-monotherapy was initiated after the first treatment management strategy to maintain a previous response, it was considered as R-maintenance rather than second-line treatment.

Overall survival (OS) was defined as the number of days from the end of the 215-day postinduction period up to and including the date of death from any cause. PFS was defined as the time from the end of the 215-day postinduction period up to and including the date of PD as assessed by the treating physician, or death from any cause. Time to next treatment (TTNT) was defined as the time from the end of the 215-day postinduction period up to and including the date of initiation of a next treatment for any reason. Patients who had not yet experienced an event at the time of analysis were censored at the date of the most recent response assessment (for PFS) or last date of contact (for TTNT and OS).

Statistical Analysis

Patient demographics, clinical characteristics at the time of diagnosis, treatment setting, induction treatment, and best response to induction treatment were summarized by group, using descriptive statistics. Pearson chi-square tests

were performed to examine the difference between R-maintenance versus observation. Logistic regression analyses were performed to identify predictors for receiving R-maintenance using backward selection ($P > .05$). Kaplan-Meier estimation was used to evaluate OS, PFS, and TTNT for the 2 groups along with the log-rank test. Cox proportional hazards models were used to compare the outcomes of R-maintenance and observation with regard to OS, PFS, and TTNT, adjusting for demographic characteristics, Follicular Lymphoma International Prognostic Index (FLIPI) risk factors, and treatment setting (region and academic/community practice). Additional sensitivity analyses were performed using propensity score methodologies to adjust for imbalances between the R-maintenance and observation groups. Sex, age, number of lymph node sites, lactate dehydrogenase level, hemoglobin level, bone marrow involvement, geographic region, practice setting, oncologist density within 50 miles, race, Eastern Cooperative Oncology Group performance status, Ann Arbor stage of disease, number of extranodal sites, histologic grade, presence of B symptoms, induction treatment, and response to the induction treatment were used to determine a propensity score for the probability of assignment to a particular treatment given the observed values. Five categories were used for induction treatment (R-monotherapy, R-CVP [rituximab plus cyclophosphamide, vincristine, and prednisone], R-CHOP [rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone], R-fludarabine, and R-other). The FLIPI risk group was not used to calculate the propensity score because individual FLIPI components were used in the model. Patients with the same propensity score had the same probability of being assigned to the particular treatment and provide comparisons that limited bias in estimating the treatment effects. In the current analysis, we defined 5 propensity score strata based on the quintiles of the propensity scores in the overall sample.

RESULTS

Of the more than 2700 patients enrolled in the NLCS between 2004 and 2007, a total of 1439 received and completed R-based induction therapy (R-monotherapy or R-chemotherapy). Of these, 1186 patients met all inclusion criteria for these analyses, as shown in Figure 1. A total of 541 patients initiated R-maintenance in the 215-day postinduction period, and 645 patients were observed. The baseline characteristics of patients who received R-maintenance or observation are shown in Table 1. Significant characteristics that were found to be

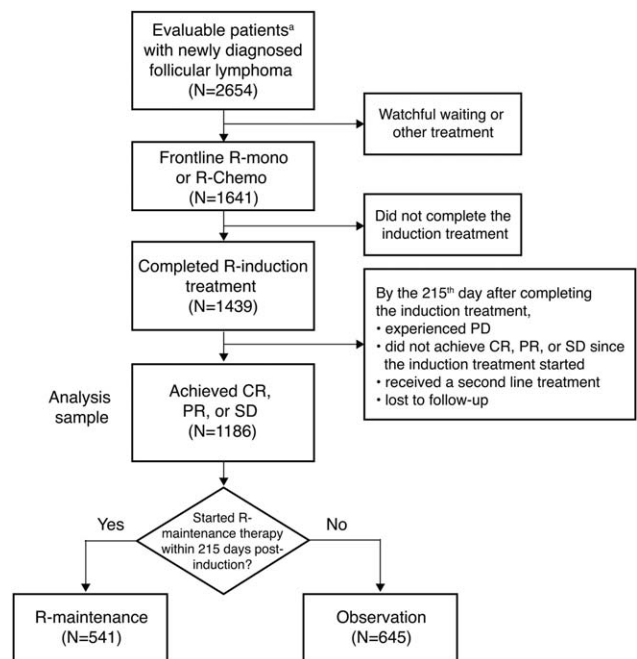


Figure 1. CONSORT (Consolidated Standards Of Reporting Trials) diagram describing the study population is shown. R-mono indicates rituximab monotherapy; R-Chemo, rituximab plus chemotherapy; R-induction, rituximab induction therapy; PD, progressive disease; CR, complete response; PR, partial response; SD, stable disease.

predictive of receiving R-maintenance based on multiple logistic regression were histology grade (1/2), Ann Arbor disease stage (III/IV), geographic region (any region other than the West), and practice setting (community practice) (Table 2).

On average, R-maintenance was initiated 113 days (interquartile range [IQR], 56 days-176 days) after the end of the R-based induction therapy, and the mean duration of R-maintenance was 546 days (IQR, 318 days-674 days). Patients received R-maintenance with several dosing schedules: R weekly for 4 weeks every 6 months (39% of patients), 1 dose every 2 or 3 months (24% of patients), or another schedule (37% of patients). Overall, 82% of patients receiving R-maintenance completed the planned maintenance therapy with a mean of 13 doses (IQR, 8 doses-16 doses). A total of 71 patients (13%) prematurely discontinued R-maintenance; 23% discontinued treatment due to PD (16 patients), 13% discontinued treatment as a result of treatment-related toxicity (9 patients; 1 patient received R-monotherapy as induction therapy and 8 patients received R-chemotherapy induction), and 8% of patients discontinued treatment due to death (6 patients). A total of 36 patients (51%) discontinued R-maintenance for other reasons, and the remaining 6% of

TABLE 1. Patient Characteristics in the R-Maintenance and Observation Groups After Achieving at Least SD With R-Based Induction

Characteristic	Observation (n=645)	R-Maintenance (n=541)	Overall (N=1186)
Median age (range) y	60 (22-96)	61 (24-97)	61 (22-97)
Male, %	48	48	48
ECOG PS, % ^a			
0	63	63	63
1	33	31	32
≥2	3	6	5
FL grade, % ^a			
1/2	72	81	76
3	29	20	24
FLIPI risk, % ^a			
Good (0-1)	33	26	30
Intermediate (2)	29	35	32
Poor (3-5)	38	39	38
Bone marrow involved, % ^a	39	41	40
Ann Arbor stage III/IV, % ^a	72	80	76
B symptoms present, %	31	27	29
Geographic region, %			
Midwest	31	33	32
Northeast	13	14	13
Southeast	32	34	33
Southwest	7	9	8
West	18	10	14
Practice setting, %			
Community	81	84	82
Induction treatment, %			
R-monotherapy	18	23	20
R-chemotherapy	82	77	80
R-CHOP ^b	58	47	53
R-CVP ^b	18	29	23
R-fludarabine ^b	15	17	16
R-other ^b	9	8	8
Response to induction			
CR or PR	89	89	89

Abbreviations: CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; FLIPI, Follicular Lymphoma International Prognostic Index; PR, partial response; R-chemotherapy, rituximab plus chemotherapy; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CVP, rituximab plus cyclophosphamide, vincristine, and prednisone; R-fludarabine, rituximab plus fludarabine-based regimen; R-maintenance, rituximab maintenance; R-monotherapy, rituximab monotherapy; R-other, rituximab plus other chemotherapy; SD, stable disease.

^aPatients with unknown classification (ECOG PS [337 patients], FL grade [117 patients], FLIPI risk [206 patients], bone marrow involvement [260 patients], and stage [9 patients]) were excluded when calculating the percentage.

^bPercentage was calculated among patients receiving R-chemotherapy, excluding 2 patients with an unclassified type of R-chemotherapy.

patients (4 patients) discontinued treatment for reasons that were unknown. Maintenance therapy was ongoing for 4% of patients in the R-maintenance group at the time of the current analysis.

At a median follow-up of 5.7 years, unadjusted PFS (188 events in the R-maintenance group and 254 events in the observed group; 5-year PFS rate: 66% vs 61%) and TTNT (130 events in the R-maintenance group and 189 events in the observed group; 5-year TTNT rate: 75% vs

TABLE 2. Factors Related to Receiving R-Maintenance Versus Observation^a

Characteristic	OR	95% CI
FL grade		
Grade 3 vs 1/2	0.60	0.45-0.81
Unknown vs 1/2	0.65	0.43-0.97
Ann Arbor stage		
III/IV vs I/II	1.69	1.28-2.24
Geographic region		
Midwest vs West	2.15	1.44-3.20
Northeast vs West	2.37	1.48-3.78
Southeast vs West	2.10	1.42-3.11
Southwest vs West	2.48	1.45-4.23
Practice setting		
Academic vs community	0.65	0.47-0.89

Abbreviations: 95% CI, 95% confidence interval; FL, follicular lymphoma; OR, odds ratio; R-maintenance, rituximab maintenance.

^aResults derived from multiple logistic regression. Patients' baseline demographic and clinical characteristics, treatment setting, and induction treatment and its response were evaluated, and nonsignificant factors were removed with backward selection ($P > .05$).

71%) were longer in the R-maintenance group compared with the observation group (Figs. 2 and 3). Unadjusted OS (79 events [3 deaths were reported as treatment related, 23 as lymphoma related, 32 as non-lymphoma related, and 21 as unknown] in the R-maintenance group vs 95 events [3 deaths reported as treatment related, 29 as lymphoma related, 38 as non-lymphoma related, and 25 as unknown] in the observed group; 5-year OS rate: 88% vs 86%) was found to be similar in the R-maintenance and observation groups (Fig. 4). After adjusting for FLIPI risk components and other factors (sex, race, histologic grade, practice setting, region, and induction treatment) in multiple variable Cox proportional hazards models, R-maintenance was found to be significantly associated with a superior PFS (hazards ratio [HR], 0.68; 95% confidence interval [95% CI], 0.56-0.84 [$P = .0003$]) and longer TTNT (HR, 0.66; 95% CI, 0.52-0.84 [$P = .0007$]). No significant difference in OS was observed between the R-maintenance and observation groups (HR, 0.81; 95% CI, 0.58-1.14 [$P = .23$]). The Cox proportional hazards model including propensity score strata demonstrated essentially the same results (Table 3). No significant effect of induction treatment on the effectiveness of maintenance therapy was observed ($P = .93$ for PFS; $P = .62$ for TTNT; and $P = .80$ for OS for the interaction term). In Cox proportional hazards models, R-maintenance appeared to have a similar impact on PFS after therapy with R-CHOP (HR, 0.71; 95% CI, 0.51-0.98) or R-monotherapy (HR, 0.62; 95% CI, 0.42-0.91) induction. No significant effect of sex on the effectiveness of maintenance therapy was observed (sex-by-maintenance/

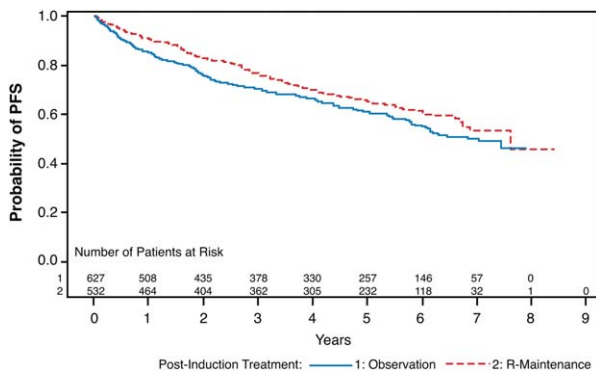


Figure 2. Progression-free survival (PFS) estimates are shown by postinduction treatment. R-Maintenance indicates rituximab maintenance.

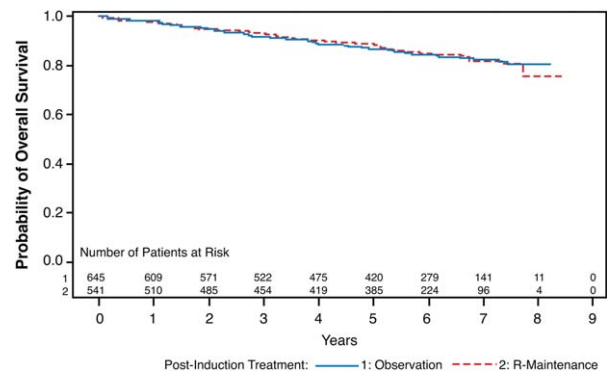


Figure 4. Kaplan-Meier estimates of overall survival are shown by postinduction treatment. R-Maintenance indicates rituximab maintenance.

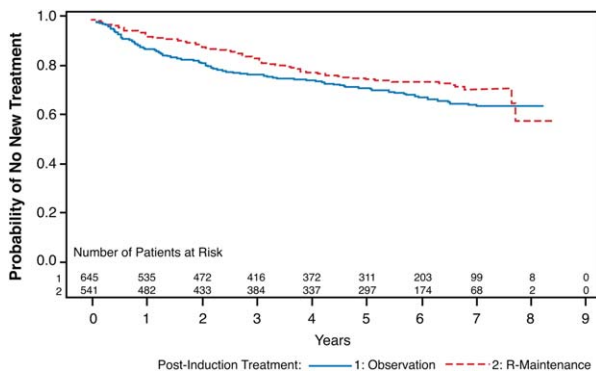


Figure 3. Time to next treatment estimates are shown by postinduction treatment. R-Maintenance indicates rituximab maintenance.

observation interaction: $P = .85$ for PFS; $P = .89$ for TTNT; and $P = .47$ for OS).

Of the patients in the R-maintenance group, 24% (130 patients) received second-line treatment (Table 4); of these patients, 36% received R-monotherapy and 31% received R-chemotherapy as second-line treatment. Of the patients in the observation group, 29% (189 patients) received second-line treatment; of these patients, 41% received R-monotherapy and 30% received R-chemotherapy. Other forms of treatment included chemotherapy, investigational therapy, radiotherapy, radioimmunotherapy, bone marrow transplant, and combination therapies. In both groups, a majority of patients (> 90%) initiated second-line treatment because of PD. The response rate for second-line treatment was similar between the R-maintenance and observation groups; 61% of patients who received maintenance therapy achieved a CR/PR with second-line treatment versus 57% in the ob-

servation arm (Table 4). In patients who received R-monotherapy as second-line treatment, the response was similar between the 2 groups ($P = .23$). Of these, 43% in the R-maintenance group achieved a CR/PR, 27% had SD, and 30% developed PD; for patients in the observation group, 58% achieved a CR/PR, 17% had SD, and 25% experienced PD. Receipt of R-maintenance was not found to be associated with inferior PFS after second-line treatment in patients who received R-containing second-line treatment (HR, 1.31; 95% CI, 0.93-1.85 [$P = .12$]).

DISCUSSION

To our knowledge, this is the largest published series of prospectively enrolled patients with previously untreated FL in the modern era examining the effectiveness of R-maintenance in clinical practice. In addition, the current study reported on the R-maintenance strategies used by practicing physicians and identified characteristics related to whether a patient received R-maintenance. This is of particular interest in that we examined practice patterns in an era of early adoption of R-maintenance after an R-based induction therapy, before published reports supporting this practice. With > 5 years of follow-up, patients who received R-maintenance after responding with at least SD after an R-based induction therapy were found to have significantly longer PFS and TTNT compared with patients who were observed. These differences occurred even with the heterogeneity in the R-maintenance schedules used. To the best of our knowledge, despite improvements in PFS and TTNT, no statistically significant difference in OS has been observed to date. If the true OS HR was 0.81, then with the current number of OS events we would only have 30% power to demonstrate an OS difference, and therefore substantially

TABLE 3. HRs for PFS, TTNT, and OS Comparing R-Maintenance With Observation

Outcomes	Cox Model Including Covariates ^a		Cox Model Including Propensity Score Strata	
	HR (95% CI)	P	HR (95% CI)	P
PFS	0.68 (0.56-0.84)	.0003	0.74 (0.61-0.90)	.003
TTNT	0.66 (0.52-0.84)	.0007	0.70 (0.55-0.88)	.0003
OS	0.81 (0.58-1.14)	.23	0.86 (0.63-1.17)	.33

Abbreviations: 95% CI, 95% confidence interval; HR, hazards ratio; OS, overall survival; PFS, progression-free survival; R-maintenance, rituximab maintenance; TTNT, time to next treatment.

^a Covariates included initial treatment, sex, race, Follicular Lymphoma International Prognostic Index (FLIPI) risk components, histologic grade, region, and practice setting (academic vs community).

longer follow-up (or a substantially larger population of FL patients in the United States) would be required to evaluate OS. Consistent results were noted after adjusting for FLIPI risk components, sex, race, histologic grade, region, treatment setting, and induction treatment using standard Cox proportional hazards models or when incorporating propensity scores.

With the expectation of FL to be highly responsive to initial therapy, coupled with disease recurrence and a shorter duration of remission with each recurrence, it is not surprising that physicians have used maintenance strategies in an attempt to extend the duration of remission. An ideal maintenance approach would be an effective therapy that is nontoxic and convenient. Because R infusion is typically well tolerated and is relatively easy to administer, it had been considered a suitable therapy to use in a maintenance regimen. We found that the use of R as a maintenance strategy after R-based induction therapy was commonly adopted by physicians in the United States in the period before the publication of the PRIMA results supporting this approach.¹¹ Presumably, this early adoption was based on several randomized controlled trials demonstrating that R-maintenance was associated with prolonged event-free survival and PFS in comparison with observation in either the first-line setting or in patients with recurrent FL.^{8,10,14} Following strategies described in these published reports, various dosing schedules were used, including a single dose administered every 2 months to 3 months or 4 weekly doses every 6 months. The majority of the patients in the current study received R-maintenance using one of these previously described dosing schedules. In addition, 37% of patients in the R-maintenance group received R-maintenance on a schedule that could not be classified as being based on a

TABLE 4. Summary of Second-Line Treatment

Second-Line Treatment	R-Maintenance (n=130)	Observation (n=189)
Second-line treatment, no. (%)		
R-monotheapy	47 (36)	78 (41)
R-chemotherapy	40 (31)	57 (30)
Chemotherapy	13 (10)	7 (4)
Investigational therapy	9 (7)	14 (7)
Radiotherapy	5 (4)	18 (10)
Radioimmunotherapy	8 (6)	9 (5)
Bone marrow transplant	1 (1)	0 (0)
CM: radiotherapy	1 (1)	1 (<1)
CM: radioimmunotherapy	1 (1)	2 (1)
CM: bone marrow transplant	3 (2)	2 (1)
Other	2 (2)	1 (<1)
Reason to start second-line treatment		
PD	125 (96)	173 (92)
Maintain a response	1 (1)	2 (1)
Other	4 (3)	14 (7)
Best response to second-line treatment		
CR/PR	72 (61)	100 (57)
SD	23 (19)	31 (18)
PD	23 (19)	44 (25)

Abbreviations: CM, combined modality; CR, complete response; PD, progressive disease; PR, partial response; R-chemotherapy, rituximab plus chemotherapy; R-maintenance, rituximab maintenance; R-monotheapy, rituximab monotheapy; SD, stable disease.

published dosing schedule, and for 4% of patients, R-maintenance was ongoing at the time of last follow-up, well beyond the 2-year duration of maintenance supported by the PRIMA study. These data highlight the challenges in applying emerging evidence regarding the efficacy of maintenance therapy to patients receiving ongoing cancer care who are in the midst of follow-up.

In addition to disease-specific features such as histologic grade (grade 1/2 FL) and stage (III/IV), practice patterns regarding R-maintenance use were found to be significantly associated with the practice setting. For example, patients who were treated in a community practice were more likely to receive R-maintenance compared with those who received treatment in an academic setting, and we also observed regional variation in the use of R-maintenance. Also of interest are the factors that were not found to be associated with receipt of R-maintenance, including FLIPI risk and degree of response to induction treatment. How these systematic variations in treatment selection impact outcomes is not well understood, and should be explored in future studies.

An alternative approach to R-maintenance is R retreatment at the time of PD, a strategy that was investigated in the randomized, phase 3 trial, ECOG 4402, Rituximab Extended Schedule or Retreatment Trial (RESORT).¹⁵ This study included asymptomatic patients with FL with low tumor burden who did not meet the

Groupe d'Etudes Lymphomes Folliculaire (GELF) criteria for treatment initiation. In this trial, patients who responded to single-agent R induction therapy were randomized to receive either R-maintenance once every 3 months or retreatment at the time of each instance of PD. Preliminary findings suggest that although patients on the maintenance therapy arm delayed time to first cytotoxic therapy compared with those on the retreatment arm, there were no differences in time to treatment failure or quality of life for patients who received R-maintenance compared with those who received R retreatment at the time of PD in this setting. To the best of our knowledge, the question of how these strategies compare in patients with FL with high tumor burden and in those receiving chemoimmunotherapy induction remains untested in randomized trials. Additional follow-up of patients in our observation group who later received single-agent R (12% currently) may provide opportunities for comparing the effectiveness of this strategy with maintenance therapy.

Another important consideration when evaluating the use of R-maintenance is the toxicity associated with extended dosing of R. In the current analysis, we explored the tolerability of R-maintenance by examining the rates of and reasons for early discontinuation of therapy. Of the 71 patients who discontinued R-maintenance (13%), 9 patients (13%) discontinued therapy because of toxicity. The risk of symptomatic hypogammaglobulinemia resulting in intravenous immunoglobulin administration in patients with B-cell lymphoma treated with multiple courses of R has been reported to be 6.6%.¹⁶ In the randomized PRIMA study, after 2 years of R-maintenance, serum concentration levels of immunoglobulin isotypes did not differ significantly between the R-maintenance and observation groups.¹¹

Concerns also have been raised regarding inducing resistance to R with extended dosing. In the current study, we examined the reasons for second-line treatment being administered and response to the various management strategies used. For the vast majority of patients in either group, second-line treatment was initiated because of PD. Approximately 24% of patients in the R-maintenance group received second-line treatment; of these, 36% received R-mono-therapy and 31% received R-chemotherapy. Similarly, in the observation group, 29% received second-line treatment; of these, 41% received R-mono-therapy and 30% received R-chemotherapy and the response was found to be similar between the 2 groups. PFS after second-line treatment containing R appeared to be similar between the 2 groups, suggesting that extended dosing of R did not appear to impact the response or duration of response to second-line treatment.

The limitations of the current study are similar to those of other observational studies, including the potential for selection bias in patient treatment choice, unmeasured confounding, and response outcome assessment based on routine clinical practice of the treating physician. In addition, data were not available to define whether patients had high or low tumor burden. Recognizing these threats, the NLCS and these analyses have been conducted in accordance with established guidelines for performing comparative effectiveness research.¹⁷⁻¹⁹ A formal study protocol including a data analysis plan was submitted before the design and execution of the current study. Analyses identified and controlled for confounding factors, an additional sensitivity analysis was performed (propensity score), and data were compared with available results from randomized clinical trials. Thus, these findings can support and augment the causal inference drawn from the results of randomized trials.

From this large, prospective, observational study with > 5 years of follow-up, we found that receipt of R-maintenance was not associated with significantly longer OS in previously untreated patients with FL who achieved at least SD after R-based induction therapy. With deaths observed in only 10% of patients in the current study, longer follow-up is needed. PFS and TTNT were found to be longer in comparison with patients in the observed group. These findings are consistent with the randomized PRIMA study, which demonstrated a significantly prolonged PFS with 2 years of R-maintenance for patients with advanced stage untreated FL who responded to an R-based induction therapy. Debate continues as to whether R-maintenance is indicated for all patients in the frontline setting or whether increasing PFS and delaying TTNT are meaningful treatment goals in selecting a maintenance strategy. The results of the current study also delineate the heterogeneity in the prescribing patterns of R-maintenance use with adoption before the publication of randomized data supporting the practice after R-based induction therapy, and suggest that significant challenges exist when applying emerging evidence from randomized clinical trials on maintenance therapy to patients receiving ongoing cancer care and follow-up.

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CONFLICT OF INTEREST DISCLOSURES

Dr. Nastoupil has received consultation fees from Genentech for work performed outside of the current study. Drs. Byrtek and Taylor and Mr. Dawson are employed by and own stock options in

Genentech. Dr. Zhou is currently conducting research for Genentech as part of employment with RTI Health Solutions. All payments are made to RTI and Dr. Zhou receives only a regular salary from RTI. Dr. Link has received grants, personal fees, and nonfinancial support from Genentech/Roche during the conduct of the current study and research funding and consulting fees from Millennium and Pharmacyclics for work performed outside of the current study. Dr. Cerhan has received reimbursement from Genentech for service on LymphoCare Scientific Advisory Board meetings performed as part of the current study. Dr. Flowers is an unpaid consultant for Genentech for service on LymphoCare Scientific Advisory Board and reports grants from Millennium/Takeda and Spectrum and other fees from Sanofi, Janssen, Abbott, Celgene, OptumRx, Seattle Genetics, and Allos Therapeutics for work performed outside of the current study.

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