Mature Results of a Phase II Study of Rituximab Therapy for Nodular Lymphocyte–Predominant Hodgkin Lymphoma

Ranjana H. Advani, Sandra J. Horning, Richard T. Hoppe, Sarah Daadi, John Allen, Yasodha Natkunam, and Nancy L. Bartlett

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ABSTRACT

Purpose
Universal expression of CD20 by malignant cells in nodular lymphocyte–predominant Hodgkin lymphoma (NLPHL) led us to evaluate rituximab (R) as a therapeutic option.

Patient and Methods
Patients with previously treated or newly diagnosed NLPHL were treated with R (375 mg/m² once per week for 4 weeks) or, after a protocol amendment, with R plus R maintenance (MR; administered once every 6 months for 2 years). Primary and secondary outcome measures were progression-free survival (PFS) and overall response rate (ORR), respectively.

Results
A total of 39 patients were enrolled (R, n = 23; R + MR, n = 16). After four once-per-week treatments, ORR was 100% (complete response, 67%; partial response, 33%). At median follow-ups of 9.8 years for R and 5 years for R + MR, median PFS were 3 and 5.6 years (P = .26), respectively; median overall survival (OS) was not reached. Estimated 5-year PFS and OS for patients treated with R versus R + MR were 39.1% (95% CI, 23.5 to 65.1) and 95.7% (95% CI, 87.7 to 100) versus 58.9% (95% CI, 38.0 to 91.2) and 85.7% (95% CI, 69.2 to 100), respectively. Nine of 23 patients experiencing relapse had evidence of transformation to aggressive B-cell lymphoma; six of these patients had infradiaphragmatic involvement at study entry.

Conclusion
R is an active agent in NLPHL. Although responses are not durable in most patients, a significant minority experience remissions lasting > 5 years. R + MR results in a nonsignificant increase in PFS compared with R. R may be considered in the relapsed setting for NLPHL. The potential for transformation of NLPHL to aggressive B-cell lymphoma underscores the importance of rebiopsy and long-term follow-up.

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INTRODUCTION

Nodular lymphocyte–predominant Hodgkin lymphoma (NLPHL) is a unique clinical entity that represents approximately 5% of Hodgkin lymphomas (HLs). The disease has a more indolent clinical behavior than classical HL (cHL), with a favorable prognosis. Despite high survival rates, late relapses are observed more frequently than in cHL. Standard treatment depends on stage and often includes radiation therapy (RT) for early-stage disease and/or chemotherapy or combined-modality therapy (CMT) according to treatment paradigms developed for cHL. Deaths resulting from NLPHL are uncommon, and treatment-related toxicities have been a major cause of mortality. Unlike cHL, the malignant cells of NLPHL universally express CD20. Therefore, targeted therapy with rituximab, a chimeric anti-CD20 monoclonal antibody, has been explored as a treatment option. We previously reported preliminary results of a phase II trial using single-agent rituximab in NLPHL administered at 375 mg/m² once per week for 4 weeks. Overall response rate (ORR) was 100%, but estimated median freedom from progression was < 1 year. On the basis of the observation in follicular lymphoma of improvement for time to treatment failure with the use of maintenance rituximab, we modified our protocol to repeat four once-per-week doses of rituximab at 6-month intervals for 2 years. Herein, we report the mature results of the phase II trial of rituximab induction with and without maintenance rituximab (MR) in NLPHL.
PATIENTS AND METHODS

This trial was initiated in 1999, and patients were treated at Stanford University Medical Center (Stanford, CA) and Washington University Medical Center (St Louis, MO). The diagnosis was confirmed in all patients by institutional pathologists by morphology and an immunohistochemistry profile of CD45+, CD20+, CD15−, and CD30− in the characteristic malignant popcorn cells. Both untreated and previously treated patients with NLPHL and Eastern Cooperative Oncology Group performance status of 0 to 2 were eligible. Measurable disease was required, with at least one lymph node measuring ≥ 1.0 cm in largest dimension or quantifiable extranodal disease. Adequate end-organ function was required: absolute neutrophil count > 1,500/mcL, platelet count > 50,000/mcL, serum creatinine level < 1.5× upper limit of normal, and liver function tests < 2× upper limit of normal.

Exclusion criteria included: RT, chemotherapy, prior rituximab treatment, or major surgery within 4 weeks of study entry. Current use of systemic glucocorticoids, any previous malignancy other than carcinoma in situ of the cervix or basal cell carcinoma of the skin in remission, serious comorbidities, or active infection also precluded eligibility. Women had to have no childbearing potential or be using adequate contraception with a negative pregnancy test at study entry. All patients provided written informed consent. The protocol was approved by the institutional review boards at both participating institutions. The study was conducted in accordance with the Declaration of Helsinki and listed on National Institutes of Health Web site clinicaltrials.gov.

All patients were evaluated within 4 weeks before initiating treatment, with routine medical history, physical examination, unilateral bone marrow biopsy, baseline laboratory tests, and baseline computed tomography (CT) scans of the neck, chest, abdomen, and pelvis to identify all sites of measurable disease. Because our study spanned almost 7 years, and imaging techniques evolved during this period, a minority of patients (n = 6) had [18F]fluorodeoxyglucose positron emission tomography–CT scans to assess disease status.

Treatment and Evaluation

The initial protocol (G7) consisted of induction therapy with rituximab 375 mg/m² administered once per week intravenously for four consecutive weeks (R). The protocol was amended in 2003 (G7B) after 23 patients had been enrolled to include maintenance dosing with rituximab at 375 mg/m² once per week for 4 weeks every 6 months for 2 years (R+). Sixteen patients were enrolled. Overall, 23 patients received R, and 16 received R+ MR. Sixteen patients were treated in the amended study.

Patients were seen during follow-up 1 month after the last dose of induction therapy, every 3 months for 18 months, and every 6 months thereafter. Repeat scans were performed at 3, 6, 12, 18, and 24 months after completion of rituximab induction. Thereafter, scans were performed per institutional standard of care. Response assessments were based on CT criteria.10 Patients with bone marrow involvement before rituximab were required to have a bone marrow biopsy to confirm complete response (CR). All relapses were confirmed by biopsy if feasible.

Statistical Methods

The primary outcome measure was progression-free survival (PFS), and secondary outcomes were CR and ORR. Response to treatment was determined for patients receiving R or R + MR on post-treatment imaging studies 3 months after the fourth dose of induction rituximab using the criteria of the National Cancer Institute Workshop.10 PFS was defined as time from the first dose of rituximab to date of confirmation of progressive disease. PFS estimates were performed with the Kaplan-Meier method using Statview 5.0 (SAS Institute, Cary, NC). Overall survival (OS) was defined as time from study entry until death resulting from any cause. Toxicity was measured using the National Cancer Institute Common Toxicity Criteria (version 2.0).

Before the amendment, for patients treated with R, a Simon two-stage optimal trial design was employed.11 It was assumed that rituximab would be of no further interest if the true ORR were ≤ 20% and would be of interest if the true response rate were ≥ 40%. For rejection of the null hypothesis, 12 responses were required among a total of 43 patients targeted for enrollment. Because the ORR after enrollment of the first 22 patients was 100%, therapy with rituximab was thought to be of sufficient interest for further study. When the study was amended to allow maintenance therapy, it was assumed that MR would be of no additional benefit if PFS at 15 months after starting treatment were ≤ 30% (null hypothesis) and of additional interest if PFS at 15 months were ≥ 65%. Using a two-sided test, 22 additional patients would be required to detect this difference, with a power of 0.80 and α = 0.05.

Patient Characteristics

From March 1999 to September 2006, 39 patients with NLPHL were enrolled. Overall, 23 patients received R, and 16 received R + MR (one patient bridged from R to amended study to receive MR). The R + MR cohort was prematurely closed because of limited funding. The characteristics of the cohorts are summarized in Table 1.

<table>
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<tr>
<th>Characteristic</th>
<th>All (N = 39)</th>
<th>Untreated (n = 12)</th>
<th>Previously Treated (n = 11)</th>
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<th>R + MR</th>
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<tr>
<td>Male sex</td>
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<tr>
<td>Age, years*</td>
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<td>2</td>
<td>9</td>
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<tr>
<td>Follow-up, years</td>
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<td>9.8</td>
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Table 1. Patient Demographic and Clinical Characteristics at Study Entry

**Abbreviations:** MR, maintenance rituximab; R, rituximab induction.

*At start of protocol treatment.
were treated with R, and nine were treated with R (range, 1 to 47 months). Twelve of these previously untreated patients from diagnosis to start of treatment in these patients was 4 months age at treatment was 38 years (range, 17 to 63 years). Median time as follows: stage I (n = 4), stage II (n = 6), stage III (n = 7). For this group, median age at treatment was 38 years (range, 17 to 63 years). Median time from diagnosis to start of treatment in these patients was 4 months (range, 1 to 47 months). Twelve of these previously untreated patients were treated with R, and nine were treated with R + MR.

Eighteen patients had received treatment for NLPHL before study entry. Details of prior therapies are listed in Appendix Table A1 (online only). Stage distribution at study entry for the latter group was as follows: stage I (n = 3), stage II (n = 9), stage III (n = 5), and stage IV (n = 1). Median time from original diagnosis of NLPHL to study entry in patients experiencing relapse was 12.7 years (range, 0.3 to 33.9 years). Median age at treatment was 44 years (range, 18 to 71 years). A total of 11 of these previously treated patients received R, and seven received R + MR.

Response, PFS, and Toxicity

All patients were evaluable for response, and ORR was 100%, with 26 patients (67%) achieving CR, and 13 (33%) achieving partial response (PR), as summarized in Table 2. No difference in ORR was observed in previously treated versus untreated patients. At median follow-ups of 9.8 years (range, 3.0 to 12.8 years) for R and 5.0 years (range, 2.5 to 8.9) for R + MR, median PFS for R and R + MR were 3.0 and 5.6 years (P = .26), respectively (Fig 1A); OS was not reached (Fig 1B). Estimated 5-year PFS and OS for patients treated with R versus R + MR were 39.1% (95% CI, 23.5 to 65.1) and 95.7% (95% CI, 87.7 to 100) versus 58.9% (95% CI, 38.0 to 91.2) and 85.7% (95% CI, 69.2 to 100), respectively. Treatment-related adverse events for both subsets were minimal, with no grade 3 or 4 toxicities.

Previously Untreated Patients

Median follow-up for patients treated with R (n = 12) was 9.5 years (range, 5.0 to 12.8 years); for those treated with R + MR (n = 9), it was 5.1 years (range, 2.5 to 8.7 years). At the end of induction therapy with four doses of R, ORR was 100% (CR, 57%), as summarized in Table 2. Median PFS for previously untreated patients treated with R and R + MR were 1.9 and 5.6 years (P = .37), respectively; median OS was not reached (Figs 2A and 2B). Median follow-up for patients without progressive disease (n = 8) at the time of this analysis was 8.1 years (range, 2.5 to 12.8 years). For patients treated with R, estimated PFS and OS at 5 years were 41.7% (95% CI, 21.3 to 81.4) and 100%, respectively. For patients treated with R + MR, estimated PFS and OS at 5 years were 51.9% (95% CI, 26.7 to 100) and 100%, respectively. There was a trend for better median PFS for patients with stage I to II versus stage III disease (5.6 and 1.8 years, respectively; log-rank P = .38). Thirteen patients experienced progression (eight of 12 treated with R; five of nine treated with R + MR). Median time to progression was 2.3 years (range, 0.9 to 6.6 years); progression was confirmed by biopsy in seven patients. Six patients (29%) experienced transformation to aggressive B-cell lymphoma at a median of 4.4 years (range, 0.9 to 7.6 years; Table 3). In four patients, aggressive histology was the first event of progression after rituximab therapy (three treated with R; one treated with R + MR); in two patients, this occurred at a median 5.3 years after progressive disease had been documented. Of note, five of the six patients with transformation had abdominal involvement at study entry (stage II with infradiaphragmatic disease, n = 1; stage III, n = 4). Of the 21 patients with previously untreated disease, three died: two resulting from relapsed transformed disease and one resulting from unknown cause.

![Fig 1. (A) Progression-free (PFS) and (B) overall survival (OS) with rituximab (R) versus R + maintenance R (MR).](image-url)
Previously Treated Patients

Median follow-up for patients treated with R (n = 11) was 9.8 years (range, 3.0 to 12.1 years); for those treated with R + MR (n = 7), it was 4.2 years (range, 3.5 to 8.9 years). At the end of induction therapy with four doses of R, ORR was 100% (CR, 78%), as summarized in Table 2. Median PFS rates for patients treated with R and R + MR were 3.4 and 6.35 years, respectively; median OS was not reached (Figs 3A and 3B). Median follow-up for patients without progressive disease (n = 8) at the time of this analysis was 5.5 years (range, 3.0 to 9.0 years). For patients treated with R and R + MR, estimated PFS rates at 5 years were 36.4% (95% CI, 16.6 to 79.5) and 71.4% (95% CI, 44.7 to 100), respectively. There was no difference in median PFS between patients with stage I to II versus stage III disease at time of rituximab therapy (4.3 and 3.4 years, respectively; P = .62; Appendix Fig A1B, online only). For patients treated with R versus R + MR, estimated OS rates at 5 years were 90.9% (95% CI, 75.0 to 100) and 71.4% (95% CI, 45 to 100), respectively. Ten patients experienced progression (seven of 11 treated with R; three of seven treated with R + MR); this was confirmed with biopsy in six patients. Median time to progression was 3.25 years (range, 0.5 to 8.6 years). Three patients (two with abdominal involvement at study entry: stage II with infra diaphragmatic, n = 1; stage III, n = 1) experienced transformation to aggressive B-cell lymphoma (biopsy proven) at a median of 7 years (range, 0.83 to 9.83 years; Table 3). In two of these patients, transformation was noted after multiple relapses with NLPHL at 84 and 117 months after study entry, respectively. Overall, four patients died, one each as a result of aggressive non-Hodgkin lymphoma (NHL), metastatic colon cancer, HL, and acute leukemia.

**Table 3. Characteristics of Patients With Transformation to Aggressive Histology**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Stage at Study Entry</th>
<th>Protocol</th>
<th>Prior Treatment (yes v no)</th>
<th>Response to Protocol</th>
<th>Time to Transformation (months)</th>
<th>Histology at Transformation</th>
<th>Treatment at Transformation</th>
<th>Current Status</th>
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<tr>
<td>Transformation as first event after protocol</td>
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<tr>
<td>1</td>
<td>IIA†</td>
<td>R</td>
<td>No</td>
<td>CR</td>
<td>74</td>
<td>Burkitt lymphoma</td>
<td>CODOX-M/IVAC</td>
<td>Alive†</td>
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<td>2</td>
<td>IIA†</td>
<td>R</td>
<td>No</td>
<td>PR</td>
<td>10</td>
<td>TCRBCL</td>
<td>CHOP</td>
<td>Dead (PD)</td>
</tr>
<tr>
<td>3</td>
<td>IIA†</td>
<td>R</td>
<td>No</td>
<td>PR</td>
<td>25</td>
<td>DLBCL</td>
<td>R-CHOP</td>
<td>Alive†</td>
</tr>
<tr>
<td>4</td>
<td>IIA†</td>
<td>R + MR</td>
<td>No</td>
<td>CR</td>
<td>66</td>
<td>DLBCL</td>
<td>CHOP</td>
<td>Dead (PD)</td>
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<tr>
<td>5</td>
<td>IIA</td>
<td>R</td>
<td>Yes</td>
<td>PR</td>
<td>9</td>
<td>TCRBCL</td>
<td>CHOP</td>
<td>Alive†</td>
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<tr>
<td>Transformation after multiple relapses after protocol</td>
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<td>6</td>
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<td>PR</td>
<td>34</td>
<td>TCRBCL</td>
<td>R-CHOP</td>
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<td>PR</td>
<td>91</td>
<td>DLBCL</td>
<td>R-CHOP, R-ICE</td>
<td>Alive†</td>
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<td>R</td>
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<td>84</td>
<td>TCRBCL</td>
<td>R-CHOP/R-ICE, SCT</td>
<td>Dead (PD)</td>
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<td>9</td>
<td>IIA</td>
<td>R</td>
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<td>PR</td>
<td>117</td>
<td>DLBCL</td>
<td>R-CHOP</td>
<td>Alive†</td>
</tr>
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Abbreviations: CHOP, cyclophosphamide, adriamycin, vincristine, and prednisone; CODOX-M/IVAC, cyclophosphamide, vincristine, doxorubicin, and high-dose methotrexate, alternating with ifosfamide, etoposide, and cytarabine; CR, complete response; DLBCL, diffuse large B-cell lymphoma; ICE, ifosfamide, carboplatin, and etoposide; MR, maintenance rituximab; PD, progressive disease; PR, partial response; R, rituximab induction; SCT, stem-cell transplantation; TCRBCL, T cell-rich B-cell lymphoma.

†From end of R treatment.
§Infradiaphragmatic disease at study entry and transformation.
No evidence of disease.
|Infradiaphragmatic disease at transformation. |
|With disease. |
(in patient previously treated with MOPP [mechlorethamine, vincristine, procarbazine, and prednisone] and RT).

**DISCUSSION**

In our series, rituximab was well tolerated and an active single agent in the treatment of NLPHL, with an ORR of 100%. A 2-year course of MR prolonged the median PFS by approximately 3 years, both in first-line and relapsed settings. The difference was not statistically significant, likely because of the small number of patients. Although the initial response was excellent, our results demonstrate a continuous pattern of relapse after R or R + MR. Importantly, approximately half of the patients treated with R + MR and one third of those treated with R remained in remission > 5 years after initiation of treatment. Although not curative, single-agent R provides substantial benefit to many patients, potentially delaying the need for cytotoxic chemotherapy. As seen in indolent NHL, the use of maintenance R in NLPHL seems to delay relapse; however, PFS rates after completion of maintenance are similar to those seen with R alone.

In contrast to cHL, there is no universal consensus regarding primary therapy for NLPHL. For patients with stage I to II disease, RT, either alone or in combination with chemotherapy, has been the mainstay of therapy, and several studies have reported excellent outcomes, with 10-year PFS > 80% to 90%.4,12-14 Because of the safety profile of rituximab, evaluation in the first-line setting is an attractive concept. Recently, the German Hodgkin Study Group (GHSG) reported on 28 patients with stage IA disease without clinical risk factors treated with four once-per-week standard doses (375 mg/m²) of rituximab. ORR was 100%; however, at a median follow-up of 3.6 years, 25% of patients had relapsed.15 Our findings for patients with previously untreated stage I to II disease are similar to those of the GHSG, with estimated 5-year PFS and OS of 56% and 87.5%, respectively. Cumulatively, these studies suggest that rituximab alone is less effective than standard RT or CMT for patients with newly diagnosed early-stage disease. Therefore, involved-field RT or CMT remains the standard of care as initial therapy for patients with stage I or II A disease.4

For patients with either advanced or limited-stage disease requiring chemotherapy, the choice of regimen varies by institution, and again, the optimal therapy is unknown.2,16,17 The largest experience of outcome is a retrospective analysis of 394 patients treated in the GHSG trials HD4 to HD12. Compared with patients with cHL, those with NLPHL had better freedom from treatment failure (88% vs 82%; P = .0092) and OS (96% vs 92%; P = .016); however, late relapses were more common.2 Retrospective studies from MD Anderson Cancer Center have reported data on the use of R-CHOP (rituximab plus cyclophosphamide, adriamycin, vincristine, and prednisone) in 15 patients with NLPHL, 11 of whom had advanced disease.17 With a median follow-up of 42 months (range, 8 to 111 months), there were no relapses or transformations, which is superior to historical data from the same institution using ABVD (doxorubicin, bleomycin, vincristine, and dacarbazine). Our results with rituximab as front-line therapy for patients with stage III or IV disease show ORR of 100%, with median PFS of 22 months (range, 8 to 74 months), suggesting that responses with rituximab are not as durable as those achieved with chemotherapy or CMT, and rituximab is not recommended as monotherapy in this setting. Therefore, chemotherapy or CMT remains the standard of care as initial therapy for advanced-stage disease unless comorbidity precludes therapy, in which case rituximab is a reasonable option.3

In our study, for patients with recurrent disease, ORR to single-agent rituximab was 100%. Treatment with R + MR resulted in an estimated 5-year PFS of 71.4% (95% CI, 44.7 to 100) and was not statistically significant compared with R (5-year PFS, 36.4%; 95% CI, 16.6 to 79.5), likely because of small patient numbers. Median OS was not reached for either R or R + MR. The GHSG has also evaluated rituximab in patients with relapsed HL.18 Fifteen patients with relapsed NLPHL received four once-per-week standard doses of rituximab. All but one patient responded to treatment, and at a median observation of 63 months, median time to progression was 33 months, and the median OS was not reached. Thus, our results as well as those from the GHSG suggest that it is reasonable to use rituximab monotherapy in the relapsed setting.

It is well recognized that there is an inherent risk for patients with NLPHL to develop aggressive B-cell NHL. Diffuse large B-cell lymphoma represents the most common histology at transformation, and a clonal relationship with NLPHL has been demonstrated.19-21 In a registry-based analysis from France between 1973 and 2003, 19 of 66
patients presented at relapse with histologic transformation to aggressive NHL at a median of 4.7 years after initial diagnosis, with inferior survival compared with patients who relapsed with NLPHL.22 The British Columbia Cancer Agency reported that with a median follow-up of 6.5 years, 13 of 95 patients with NLPHL experienced transformation to aggressive NHL, with actuarial risks for transformation after initial diagnosis of NLPHL of 5% and 31% after 5 and 20 years, respectively. Additionally, transformation was more likely in patients with initial splenic involvement (P = .006).23 In our series, overall, nine of 23 patients had evidence of transformation to aggressive B-cell lymphoma at relapse. Of these, six patients treated with rituximab as initial therapy experienced transformation, four within the first 5 years. This transformation seen in our study was higher than those reported by other series. Of note, six of the nine patients experiencing transformation had infradiaphragmatic disease at study entry. It is possible that these patients had a concurrent aggressive histology at the outset that was only partially treated with rituximab. Median OS of these patients after transformation was 52 months (range, 2 to 143 months), consistent with that reported in the literature, which suggests that 10-year OS post-transformation is approximately 60%.24 Collectively, our data and those from other series underscore the importance of long-term follow-up of patients with NLPHL, with special consideration given to biopsy infradiaphragmatic disease both at diagnosis and at relapse.

In conclusion, rituximab is an active agent in both untreated and relapsed NLPHL. Maintenance rituximab seems to prolong remission, similar to results in indolent NHL, but our small patient numbers preclude definitive conclusions. Single-agent rituximab is not curative for NLPHL and therefore should be considered primarily in the management of patients in the relapse setting. Given the low incidence of NLPHL, randomized trials in this disease are challenging; however, because of the high single-agent response rate and safety profile, incorporating rituximab into a chemoimmunotherapy regimen for NLPHL, as is standard for B-cell NHLs, is a reasonable consideration for future clinical investigation.

Although all authors completed the disclosure declaration, the following author(s) and/or an author’s immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a “U” are those for which no compensation was received; those relationships marked with a “C” were compensated. For a detailed description of the disclosure categories, or for more information about ASCO’s conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

**Employment or Leadership Position:** Sandra J. Horning, Genentech (C);
Consultant or Advisory Role: Ranjana H. Advani, Genentech (U);
Richard T. Hoppe, Clarient (C);
Stock Ownership: Sandra J. Horning, Roche Honorary; Richart T. Hoppe, Clarient Research Funding: Ranjana H. Advani, Genentech Expert Testimony: None Patents, Royalties, and Licenses: None Other Remuneration: None.

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Collection and assembly of data: Ranjana H. Advani, Sandra J. Horning, Richard T. Hoppe, Sarah Daadi, John Allen, Nancy L. Bartlett
Data analysis and interpretation: Ranjana H. Advani, Sandra J. Horning, Richard T. Hoppe, John Allen, Yasodha Natkunam, Nancy L. Bartlett

**REFERENCES**


GLOSSARY TERMS

**CD20**: Cell-surface antigen present on lymphoid B cells. CD20 is a widely used phenotypic marker for typing malignant lymphomas. It is involved in B-cell activation.

**Monoclonal antibody**: An antibody that is secreted from a single clone of an antibody-forming cell. Large quantities of monoclonal antibodies are produced from hybridomas, which are produced by fusing single antibody-forming cells to tumor cells. The process is initiated with initial immunization against a particular antigen, stimulating the production of antibodies targeted to different epitopes of the antigen. Antibody-forming cells are subsequently isolated from the spleen. By fusing each antibody-forming cell to tumor cells, hybridomas can each be generated with a different specificity and targeted against a different epitope of the antigen.
Appendix

Table A1. Prior Therapies

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<th>Patient No.</th>
<th>Protocol</th>
<th>Prior Treatment</th>
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<td>17</td>
<td>R + MR</td>
<td>RT</td>
</tr>
<tr>
<td>18</td>
<td>R + MR</td>
<td>MOPP/ABV, RT</td>
</tr>
</tbody>
</table>

Abbreviations: ABV, doxorubicin, bleomycin, and vinblastine; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; ASCT, autologous stem-cell transplantation; ChlVPP, chlorambucil, vinblastine, procarbazine, and prednisone; MOPP, mechlorethamine, vincristine, procarbazine, and prednisone; MR, maintenance rituximab; R, rituximab; RT, radiation therapy.

Fig A1. Progression-free survival in previously (A) untreated and (B) treated patients by stage.