

Reassessing the Standard of Care in Indolent Lymphoma: A Clinical Update to Improve Clinical Practice

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Key Words

Non-Hodgkin's lymphoma, NHL, diffuse large B-cell lymphoma, follicular lymphoma, chronic lymphocytic leukemia, small lymphocytic lymphoma, CLL, SLL, Waldenström's macroglobulinemia

Abstract

Non-Hodgkin's lymphoma (NHL) represents a diverse group of hematologic malignancies originating in B or T lymphocytes. Approximately 85% of NHLs are of B-cell origin, with the remainder mostly of T-cell origin. The most common NHL types are diffuse large B-cell lymphoma (31%) and follicular lymphoma (22%). More than 65,000 new cases of NHL develop each year, and approximately 20,000 people with NHL died of the disease 2009. NHL is the seventh most common cancer in the United States, contributes to approximately 4% to 5% of all cancer cases in the United States, and causes approximately 3% of all cancer-related deaths. Currently, nearly 500,000 people are living with the disease or are in remission. Several new and encouraging advances have been made in the treatment of indolent NHL. Although the watch and wait approach still has a role, combined immunochemotherapy remains the standard of care for both first-line and relapsed/refractory disease. As front-line treatment, bendamustine plus rituximab may become a new standard of care, especially for older patients. In contrast, rituximab in combination with chemotherapy followed by rituximab maintenance seems to be the optimal option in patients with relapsed disease. (*JNCCN* 2010;8[Suppl 6]:S1-S14)

Epidemiology

Non-Hodgkin's lymphoma (NHL) represents a diverse group of hematologic malignancies originating in B or T lymphocytes. Approximately 85% of NHLs are of B-cell origin, with the remainder mostly of T-cell origin.¹ The most common NHL types are diffuse large B-cell lymphoma (DLBCL; 31%) and follicular lymphoma (FL; 22%; (Figure 1).²

More than 65,000 new cases of NHL develop each year, and approximately 20,000 people with NHL will

die in 2009.³ NHL is the seventh most common cancer in the United States, contributes to approximately 4% to 5% of all cancer cases in the United States, and causes approximately 3% of all cancer-related deaths.^{1,4} Currently, nearly 500,000 people are living with the disease or are in remission.⁴

The age-adjusted incidence of NHL increased more than 75% from 1975 to 2006.⁴ In addition, the incidence of NHL increases with age. The incidence increases approximately 20-fold between the ages of 20 to 24 years and 60 years, and about 50-fold between the ages of 20 to 24 years and 75 years. The prevalence of histologic subtypes also varies depending on age group.⁵

Pathophysiology and Classification

NHL is classified as indolent, aggressive, or highly aggressive. Indolent lymphoma subtypes include FL, chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), and marginal zone lymphoma (MZL), which includes mucosa-associated lymphoid tissue (MALT) lymphoma, splenic MZL, and nodal MZL.¹ Lymphoplasmacytic lymphoma, also termed Waldenström's macroglobulinemia (WM), is also considered to be an indolent form of NHL.⁶ Aggressive NHLs include DLBCL and mantle cell lymphoma (MCL). Highly aggressive NHLs include Burkitt's lymphoma, lymphoblastic lymphoma, and AIDS-related B-cell lymphoma.⁶ This clinical update focuses on indolent NHL.

The causes of NHL are mostly unknown, and those that are known explain only a small proportion of cases.⁴ Immunosuppression may be involved, as evidenced by the association of HIV infection with a higher incidence of NHL. In addition, exposure to herbicides, pesticides, and certain viruses such as Epstein-Barr virus

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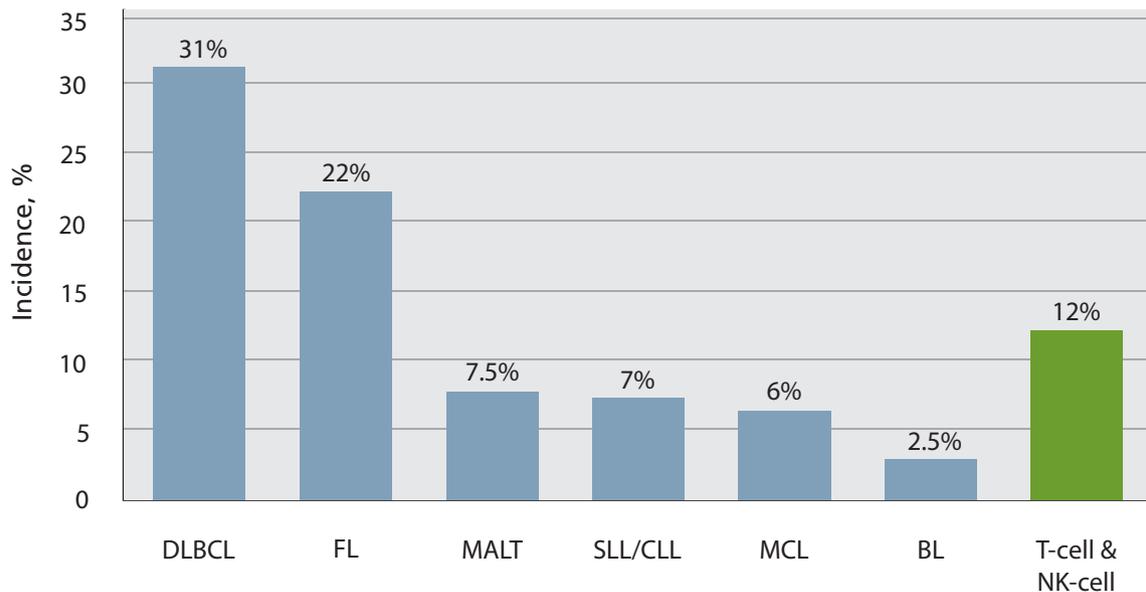


Figure 1. Non-Hodgkin's lymphoma types and prevalence. BL, Burkitt's lymphoma; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MALT, mucosa-associated lymphoid tissue; MCL, mantle cell lymphoma; NK, natural killer; SLL, small lymphocytic lymphoma.

and human T-lymphotropic virus have also been associated with a higher incidence of NHL. In addition, the bacterium *Helicobacter pylori* is associated with the development of MALT lymphoma in the stomach wall. Some forms of lymphoma may also have a genetic basis. Recent progress was made in understanding the molecular pathogenesis of lymphoid malignancies based on morphologic, immunophenotypic, and clinical parameters (Table 1).

Follicular Lymphoma

In general, FL progresses slowly and is characterized by a t(14;18)(q32;q21) translocation, which leads to overexpression of antiapoptotic B-cell lymphoma 2 protein in approximately 90% of cells. The disease proliferates in a network of nonmalignant follicular dendritic and T cells.⁷ In addition, a small fraction of cells exhibit alterations leading to changes in B-cell lymphoma 6 expression. Typically, cells are CD10+, CD19+, CD20+, CD22+, CD38+, CD40+, CD86+, CD95+, and surface immunoglobulin M (IgM) > IgG > IgA.⁷

The WHO revised the classification of lymphomas in the 4th edition of the *Classification of Tumours of Haematopoietic and Lymphoid Tissues*, published in 2008, updating information published in 2001.⁸ In the revised version, the classification of the most common lymphoma subtypes, FL and DLBCL, was altered to enhance diagnostic accuracy and aid in clinical man-

agement.⁹ Until recently, FL was conventionally graded according to the proportion of centroblasts and, based on this, stratified into 3 grades. However, inaccurate classification and the clinical relevance of separating grades 1 and 2 have been questioned because of minimal differences in long-term outcome observed between these grades. Consequently, the 2008 WHO classification describes cases with few centroblasts as "FL grade 1-2 (low grade)" and does not require or recommend further separation.⁹ The classification also recommends stratifying grade 3 FL according to the presence or absence of residual centrocytes (3A vs. 3B, DLBCL-like subtype), which was optional in the 2001 WHO classification but is now mandatory.⁸

Chronic Lymphocytic Leukemia/ Small Lymphocytic Lymphoma

CLL/SLL can be identified by the immunophenotype CD5+, CD10-, CD19+, CD20+, dim expression of surface immunoglobulin, CD23+, CD43 +/-, and cyclin D1-.¹ The absence of cyclin D1 is critical in distinguishing CLL/SLL from MCL. A favorable prognosis in CLL/SLL is associated with the presence of a mutated immunoglobulin heavy chain variable region, and low CD38 and zeta-chain-associated protein kinase 70 protein expression. Chromosomal aberrations in CLL include del 6q, del 11q, del 13q, trisomy 12, and del 17p.¹

Table 1 Pathogenetic Insights Based on a Disease-Oriented Approach to Lymphoma Classification

<i>Lymphomas associated with infectious agents</i>	
Nasal, cutaneous and systemic NK/T-cell lymphomas	EBV
Adult T-cell leukemia/lymphoma	HTLV1
Marginal zone lymphomas	<i>Helicobacter pylori</i> , <i>Borrelia burgdorferi</i> , <i>Campylobacter jejuni</i> , hepatitis C, and others
Primary effusion lymphoma, LBCL associated with multicentric CD	HHV-8/KSHV
Plasmablastic, Burkitt's, DLBCL, CHL	EBV (subset of cases)
<i>Lymphomas with deregulation of apoptosis and survival pathways</i>	
Follicular lymphoma	<i>BCL2/IIGH@</i>
MALT lymphomas	<i>API2/MALT1</i> and variants
<i>Lymphomas with deregulation of the cell cycle</i>	
Mantle cell lymphoma	<i>CCND1/IIGH@</i>
Burkitt's lymphoma	<i>MYC/IIGH@</i> and variants
<i>Lymphomas with deregulation of cell signaling or transcriptional regulation</i>	
Anaplastic large cell lymphoma	<i>NPM/ALK</i> and variants
Diffuse large B-cell lymphomas	<i>BCL6</i> , NF- κ B, Stat6
Lymphomas associated with host susceptibility factors, congenital or acquired	Genetics, gliadin allergy
Enteropathy-associated T-cell lymphoma	Genetics, host response to EBV
<i>Extranodal and systemic EBV + TINK cell lymphomas</i>	
Hepatosplenic T-cell lymphoma	Immunosuppression combined with chronic antigenic stimulation
<i>Lymphomatoid granulomatosis</i>	
Burkitt's lymphoma	Partial immune dysfunction and EBV
Posttransplantation and other iatrogenic lymphoproliferative disorders	Polyclonal B-cell activation with or without immunosuppression (malaria, HIV) Iatrogenic immunosuppression

Abbreviations: EBV, Epstein-Barr virus; CD, Castleman's disease; CHL, classic Hodgkin's lymphoma; DLBCL, diffuse large B-cell lymphoma; HHV-8, human herpesvirus 8; HTLV1, human T-lymphotropic virus Type 1; KSHV, Kaposi's sarcoma-associated herpesvirus; LBCL, large B-cell lymphoma; MALT, mucosa-associated lymphoid tissue; NF- κ B, NF kappa B cells; NK, natural killer. Adapted from Jaffe ES, Harris NL, Stein H, Isaacson PG. Classification of lymphoid neoplasms: the microscope as a tool for disease discovery. *Blood* 2008;112:43845; with permission.

Marginal Zone Lymphoma

Marginal zone B-cell lymphomas originate from B lymphocytes normally present in a distinct anatomic location known as the *marginal zone*. Marginal zone areas are present in lymphoid organs, such as the spleen and lymph node, and in nonlymphoid organs, for example, the MALT. Nonmucosal tissue such as skin and the orbit and dura can also be involved. MZL has been classified into 3 subtypes: extranodal MZL of MALT type, splenic MZL (with or without villous lymphocytes), and nodal MZL (with or without monocytoid B cells).¹⁰

MZL diagnosis can be established with immunophenotyping, which shows the following features: CD5–, CD10–, CD19+, CD20+, CD23–, cyclin D1,

and bcl-2 follicles. Splenic MZL is additionally negative for annexin-1 and CD103. Molecular evaluation with fluorescence in situ hybridization or cytogenetics to determine chromosomal translocation t(11;18) can further confirm MZL diagnosis.¹

Waldenström's Macroglobulinemia

WM is characterized by excess lymphoplasmacytic cells in the bone marrow, hyperproduction of IgM, and involvement of visceral organs, including the spleen and liver.^{6,11} The overall incidence is approximately 3 per million persons per year, representing approximately 1% to 2% of hematologic malignancies.¹¹ Patients typically present with anemia, splenomegaly, or lymphadenopathy. WM also can in-

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crease serum viscosity, which predisposes patients to neurologic complications. In addition, bone marrow mast cells overexpress the CD40 ligand (CD154), which is a potent inducer of B-cell expansion. The origin of WM is poorly understood and considered to be mostly sporadic, but multigenerational clustering and familial patterns indicate the possible role of inherited factors.¹¹

Current Standard Treatment of Front-Line and Refractory Indolent NHL

No standard therapy exists for the first-line treatment of indolent lymphoma, which was highlighted by the findings of the National LymphoCare Study,¹² a registry of patients with newly diagnosed FL. The study showed that approaches to the treatment of patients with FL are widely disparate. Of the 2728 subjects, approximately half (51.9%) were initially treated with chemotherapy plus rituximab; the rest were observed (17.7%), treated with rituximab monotherapy (13.9%), entered into a clinical trial (6.1%), or treated with radiation therapy (5.6%) and chemotherapy only (3.2%). The most common forms of chemotherapy used in combination with rituximab were CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone; 55%), CVP (cyclophosphamide, vincristine, and prednisone; 23.1%), and fludarabine-based chemotherapy (15.5%).

Observation until development of symptoms or progression may be warranted before treatment in patients with a low-risk Follicular Lymphoma International Prognostic Index (FLIPI) score. If the goal of therapy is complete remission, as is often the case for younger, physically fit patients, a more aggressive approach can be used. A less aggressive approach may be selected for older patients, who usually are less able to tolerate aggressive therapy.

The introduction of chemoimmunotherapy, which has been shown to improve survival, has changed the natural history of indolent lymphoma.¹³ However, several unanswered issues remain, such as how to select the optimal first-line and salvage treatments, the role of maintenance therapy, and the role of stem cell transplantation.¹³

Benefits of Adding Rituximab

The most widely used front-line treatment for patients with FL is rituximab in combination with chemotherapy.¹² Although the optimal chemotherapy to

use with rituximab remains unclear, many randomized studies indicate that combining rituximab with chemotherapy provides a substantial benefit compared with chemotherapy alone, in both the front-line and relapsed/refractory settings.^{14,15}

In a meta-analysis of patients with newly diagnosed indolent or MCL, rituximab in combination with chemotherapy was shown to improve overall survival compared with chemotherapy alone.¹⁶ The analysis included 1943 patients in 7 randomized controlled trials reported from January 1990 to December 2005. Patients treated with rituximab had a lower hazard ratio (HR) for mortality than those receiving chemotherapy alone (0.65; 95% CI, 0.54–0.78). Overall response and disease control were also significantly superior with rituximab plus chemotherapy.

Rituximab also seems to be effective against other indolent NHL, including MZL, WM, and SLL,^{17,18} and rituximab plus chemotherapy also increases response rates and prolongs survival among patients with CLL.^{19–21}

Role of Maintenance Rituximab

Maintenance therapy with rituximab, either as 4 weekly infusions every 6 months or as a single infusion every 2 to 3 months, seems to improve outcomes in patients with FL, although the benefit is more clearly established for the relapsed/refractory^{22,23} than for the front-line setting. In the relapsed/refractory setting, Van Oers et al.²² reported improved progression-free survival after induction with both CHOP (HR, 0.30; $P < .001$) and R-CHOP (HR, 0.54; $P = .004$). In addition, rituximab maintenance improved overall survival from second randomization (85% at 3 years vs. 77% with observation; HR, 0.52; $P = .011$). Likewise, Forstpointner et al.²³ reported a significantly prolonged response duration with rituximab maintenance after rituximab-FCM (fludarabine, cyclophosphamide, mitoxantrone) in the relapsed/refractory setting, with a benefit for both patients with FL or MCL when analyzed separately.

The benefit for maintenance rituximab in the relapsed/refractory setting was further established in a recent meta-analysis of randomized controlled trials comparing rituximab maintenance therapy with observation or treatment at relapse (Figure 2).²⁴ Five trials of 1143 adult patients were included; of those, 985 patients had FL and were evaluable for overall survival. Overall, maintenance rituximab was associated with an HR for death of 0.60 (95% CI,

0.45–0.79). However, the rate of infection-related adverse events was higher with rituximab maintenance treatment (HR, 1.99; 95% CI, 1.21–3.27). In patients with relapsed/refractory FL, the survival benefit was significantly improved with maintenance rituximab (HR for death, 0.58; 95% CI, 0.42–0.79), whereas for previously untreated patients with FL, no significant survival benefit was observed (HR for death, 0.68; 95% CI, 0.37–1.25).

The usefulness of maintenance rituximab has also been evaluated in the front-line setting in the PRIMA study. The recently presented data show a clear benefit of rituximab maintenance.^{25,26} Rituximab plus CHOP, CVP, or FCM chemotherapy was used as initial treatment. Patients who experienced response were randomly assigned to receive rituximab alone, given once every 2 months for 2 years, or observation alone (Figure 3A). Two years of rituximab maintenance therapy after induction immunochemotherapy in previously untreated patients with FL significantly improves progression-free survival compared with observation (82%; 95% CI, 78%–86% vs. 66%; 95% CI, 61%–70%) with little additional toxicity (Figure 3B). These data may provide a basis for a new standard of care for patients with FL. A 2-year maintenance therapy also recently showed superior progression-free survival in patients with relapsed FL.²⁷

Radioimmunotherapy

Radioimmunotherapy remains a cornerstone of treatment for patients with indolent lymphoma in the front-line setting.²⁸ Two commercially available radioimmunoconjugates that target CD20, yttrium-90 (⁹⁰Y)-labeled ibritumomab tiuxetan and iodine-131 (¹³¹I)-labeled tositumomab, are approved for use in patients with relapsed or refractory follicular or low-grade NHL.

In the first-line setting, these agents have been studied as monotherapy and also as consolidation after initial chemotherapy. In the international European FIT trial,²⁹ ibritumomab tiuxetan was evaluated in patients undergoing various different induction chemotherapy regimens (< 20% received rituximab-containing regimens). A total of 414 patients who achieved a partial response or better after first-line induction treatment were randomly assigned to receive radioimmunotherapy plus rituximab or no further treatment. After a median follow-up of 3.5 years, ibritumomab tiuxetan consolidation, compared with no further treatment, significantly prolonged median progression-free survival in all patients (36.5 vs. 13.3 months; HR, 0.465; $P < .0001$). Ibritumomab tiuxetan was more effective than no further treatment regardless of whether a complete or partial response was achieved after induction treatment and in all FLIPI

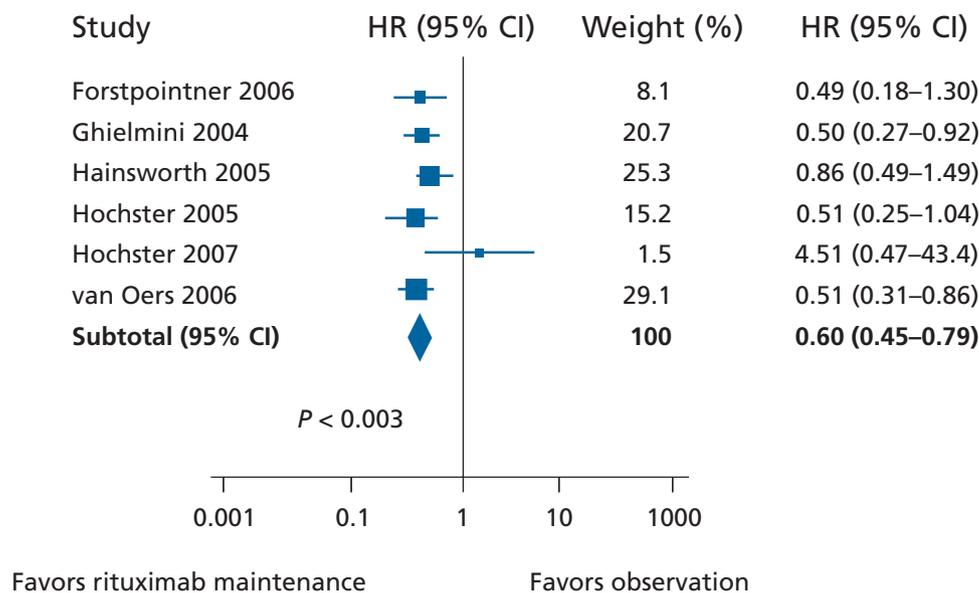


Figure 2. Benefit of maintenance rituximab in follicular lymphoma. CI, confidence interval; HR, hazard ratio. Adapted from Salles GA, Seymour JF, Feugier P, et al. Rituximab maintenance for 2 years in patients with untreated high tumor burden follicular lymphoma after response to immunochemotherapy. Presented at the 2010 Annual Meeting of the American Society of Clinical Oncology; June 4-8, 2010; Chicago, Illinois. Abstract 8004.

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risk groups. In addition, 77% of patients who had a partial response after induction converted to a complete response, for a final complete response rate of 87%. Observed toxicity was mostly hematologic.

Similarly, for tositumomab, the phase II SWOG S9911 trial showed excellent results in patients with previously untreated, advanced-stage FL.³⁰ The study included 90 patients receiving 6 cycles of CHOP chemotherapy followed 4 to 8 weeks later by tositumomab. The overall response rate was 91%, which included a 69% complete response rate. At a median follow-up of approximately 5 years, the overall and progression-free survival rates were 87% and 67%, respectively.

A large randomized trial is comparing R-CHOP and CHOP followed by tositumomab, with results expected shortly.³¹ SWOG is also currently evaluating R-CHOP followed by tositumomab plus maintenance with rituximab.³²

In 2005, initial results were reported in patients with previously untreated stage III and IV FL receiving a single course of tositumomab.³³ Patients were followed after disease progression or after 2 years on study. The initial overall response rate in 76 patients was 97%, with 75% experiencing a complete response.³³ After a median of 10 years of follow-up (range, 0.7–12.3 years), the median duration of response was 6 years (95% CI, 2.5–10.8), with approximately 40% remaining progression-free at 10 years.³⁴ Of the 57 patients with a complete response, median progression-free survival was 10.9 years, with a 10-year overall survival rate of 82%. Given that patients receive only one course of therapy, this treatment approach is therefore very acceptable to patients.

Treatment of CLL

CLL that has progressed after initial locoregional radiation therapy or is diagnosed at an advanced stage can be treated with chemoimmunotherapy or chemotherapy. Chemotherapy regimens that have shown efficacy in clinical trials include chlorambucil or cyclophosphamide given with or without prednisone, purine analogs, or an alkylating agent-based combination regimen such as CHOP.¹

Two large randomized trials, the U.S. Intergroup E2997 and the United Kingdom Leukemia Research Fund CLL 4, have shown that fludarabine combined with cyclophosphamide was associated with an increased response and progression-free survival compared with fludarabine alone.^{35,36} In addition, an

analysis of data from the E2997 trial indicated that mutated immunoglobulin heavy chain variable region, CD38, or zeta-chain-associated protein kinase 70 expression did not predict outcome of fludarabine-based therapy.³⁷

As in other indolent lymphomas, rituximab has shown improved outcomes in CLL when used in combination with chemotherapy. The CALGB 9712 study found that concurrent administration of rituximab in combination with fludarabine was associated with a higher overall response rate than sequential administration of these agents in patients with previously untreated CLL (90% vs. 77%, respectively).³⁸ The addition of rituximab to fludarabine was also found to prolong overall and progression-free survival in a retrospective comparison of the CALGB 9712 and 9011 trials.³⁹

The combination of fludarabine, cyclophosphamide, and rituximab (FCR) has also been found to produce a high overall response rate both as initial therapy and also in the relapsed/refractory setting.^{40,41} A recent randomized trial (CLL8) conducted in Germany compared FC with FCR and showed a significant improvement in complete response and overall survival in patients treated with FCR compared with FC.²¹

The FDA recently approved an oral form of fludarabine as a single agent in CLL, which may be especially useful in patients unable to receive intravenous administration. In addition, in February 2010, the FDA officially approved rituximab in the treatment of CLL when combined with FC (i.e., FCR) for use in both the front-line and relapsed/refractory settings, even though it was already widely used off-label for this purpose.

Treatment of WM

In an article describing his approach to treating patients with WM, Treon⁴² suggests that asymptomatic patients should be observed only, whereas treatment should be considered in patients with various symptoms, including hemoglobin level less than 10 g/L, platelet count less than $100 \times 10^9/L$, bulky adenopathy or organomegaly, symptomatic hyperviscosity, or peripheral neuropathy. Plasmapheresis should be considered in patients with symptomatic hyperviscosity and in those for whom rituximab might be used.

Fludarabine and rituximab are highly active in patients with WM. Treon et al.⁴³ studied this combination in 43 patients with WM who had received

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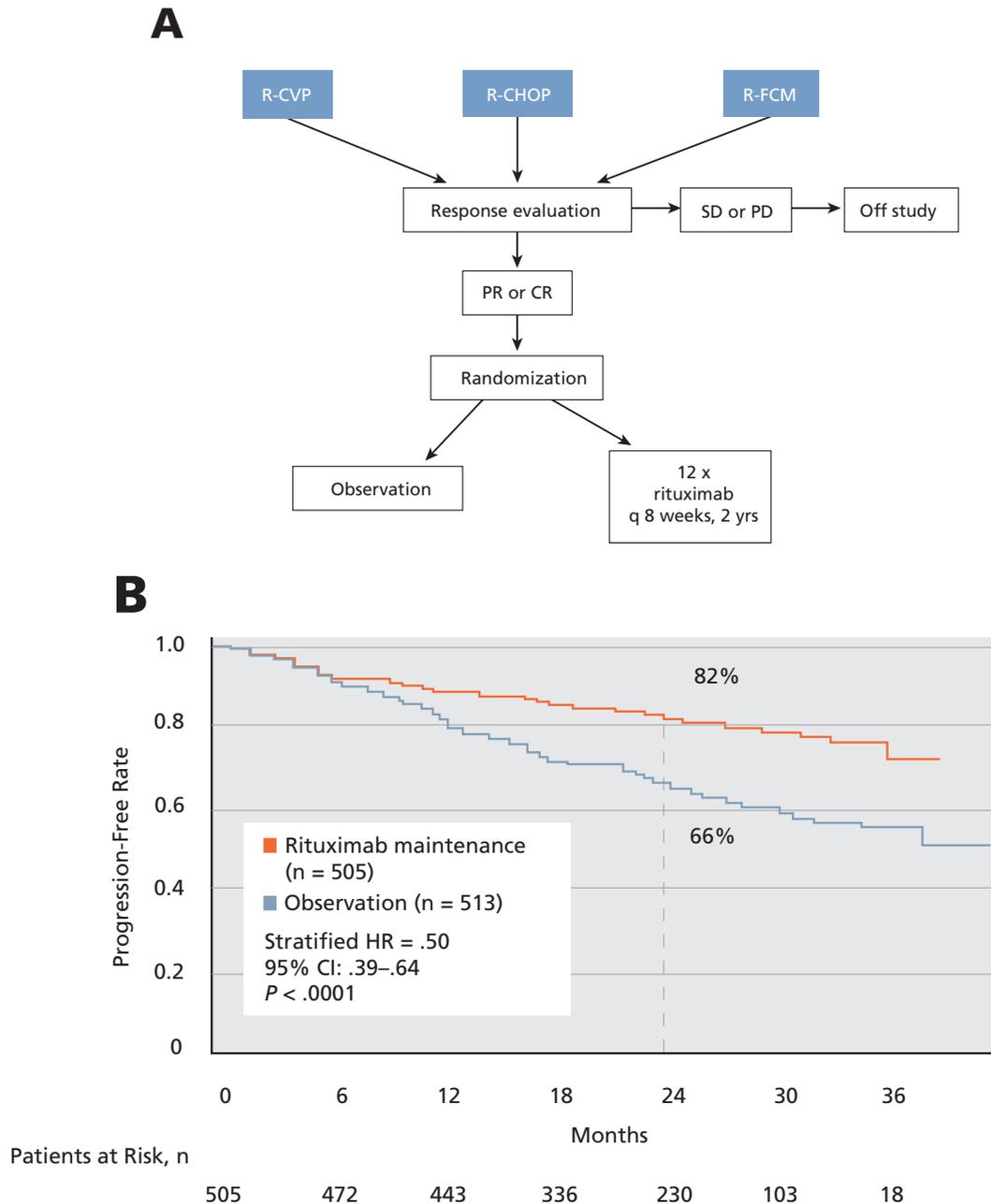


Figure 3. (A) Design of the PRIMA trial. CR, complete response; PD, progressive disease; PR, partial response; R-CHOP, rituximab + cyclophosphamide, doxorubicin, vincristine, prednisone; R-CVP, rituximab + cyclophosphamide, vincristine, and prednisone; R-FCM, rituximab + fludarabine, cyclophosphamide, mitoxantrone; SD, stable disease. (B) PRIMA trial results. CI, confidence interval; HR, hazard ratio.

less than 2 prior therapies. Therapy consisted of 6 cycles of fludarabine at a dose of 25 mg/m²/d for 5 days and 8 infusions of rituximab at a dose of 375 mg/m²/wk. Sixteen patients had a complete or very good partial response, with an overall response rate of 95.3% (major response, 86.0%). Toxicities were mostly hematologic and caused by infections. Grade

3 or higher toxicities included neutropenia (n = 27), thrombocytopenia (n = 7), and pneumonia (n = 6), including 2 patients who died of non-*Pneumocystis carinii* pneumonia, suggesting that the risk for toxicities associated with treatment must be considered along with the potential benefits.

Recently, the mammalian target of rapamycin

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inhibitor, everolimus, was evaluated in a phase II trial of relapsed/refractory WM.⁴⁴ A total of 50 patients with measurable WM (IgM monoclonal protein > 1000 mg/dL with > 10% marrow involvement or nodal masses > 2 cm) received 10 mg/d everolimus. The overall response rate was 70% (95% CI, 55%–82%), with a partial response rate of 42% and a 28% minimal response, suggesting an encouraging level of activity for this agent. The estimated progression-free survival rate at 12 months was 62% (95% CI, 48%–80%). The most common toxicities were hematologic.

Another study evaluated bortezomib and rituximab in patients with relapsed/refractory WM who had received at least one previous treatment and found the combination to be highly active.⁴⁵ Patients were treated with 6 cycles of bortezomib, 1.6 mg/m², on days 1, 8, and 15, every 28 days. Rituximab was given at a dose of 375 mg/m²/wk along with bortezomib in cycles 1 and 4. The median progression-free survival was 15.6 months (95% CI, 11–21 months), with estimated 12- and 18-month progression-free survival rates of 57% (95% CI, 39%–75%) and 45% (95% CI, 27%–63%), respectively. Side effects were mostly associated with infections or were hematologic in nature. Grade 3 peripheral neuropathy was noted in 2 patients (5%).

New Agents in Indolent Lymphoma

New agents of interest in indolent NHL include bendamustine, lenalidomide, and bortezomib. Several other agents are in earlier-stage clinical trials.

Bendamustine

Unlike typical DNA-alkylating agents, bendamustine, a purine analog–like alkylator, mediates activation of DNA-damage stress response and apoptosis, inhibition of mitotic checkpoints, induction of mitotic catastrophe, and induction of a base excision DNA repair pathway.⁴⁶ In addition, bendamustine has shown nonresistance with typical DNA-alkylating agents.⁴⁷ The clinical activity of bendamustine in patients with NHL has been established for more than 3 decades in Europe and recently also in the United States. Bendamustine is currently approved to treat patients with CLL and indolent B-cell NHL whose disease has progressed during or within 6 months of treatment with a rituximab-containing regimen. Recently, however, studies have shown re-

sponses of more than 70% in patients with chemotherapy- and rituximab-refractory disease, suggesting that bendamustine is highly effective in this setting. Moreover, when bendamustine is combined with rituximab in previously untreated patients, responses of more than 90% have been reported.⁴⁸ Bendamustine has also shown superior efficacy when compared with chlorambucil in patients with CLL.⁴⁹

A recent study⁴⁸ reported at the American Society of Hematology (ASH) 2009 annual meeting compared 6 cycles of bendamustine-rituximab (BR) with 6 cycles of rituximab-CHOP (R-CHOP) as first-line therapy in patients with FL, other types of indolent lymphoma, and MCL. Among 513 randomly assigned and evaluable patients, BR was both less toxic and more effective than R-CHOP, with a median progression-free survival of 54.9 months for BR versus 34.8 months with R-CHOP ($P = .0002$; HR, 0.57) at a median follow-up of 34 months (Figure 4). Moreover, the benefit observed with bendamustine extended to all risk groups and to most subtypes (except MZL; Figure 5). Patients with grade 3 FL were not included in this trial, but it is very possible that these patients would also benefit from the BR regimen.⁵⁰ Overall survival was not significantly different between groups.

More adverse events, including grade 3/4 neutropenia, were noted with R-CHOP (46.5%) compared with BR (10.7%). In a study of previously treated patients with NHL, the BR combination proved to be a highly active regimen, showing an overall response rate greater than 90%. Men and patients with stage IV disease were less likely to experience a complete response.⁵¹

Additionally, a substudy of the trial of bendamustine showed that in young patients the BR combination did not seem to impair the collection of stem cells for subsequent transplant.⁵² The study found that the mobilization ability was similar in both arms.

Lenalidomide

Lenalidomide, an analog of the immunomodulatory drug thalidomide, is approved in combination with dexamethasone for treating patients with multiple myeloma. This agent is also indicated for the treatment of people with myelodysplastic syndromes with a deletion of chromosome 5q. Lenalidomide has also shown promise in the treatment of patients with indolent lymphomas. Treatment of patients with relapsed/refractory lymphoma using single-agent le-

lenalidomide achieved a modest overall response rate of 23%, but these responses were durable, lasting more than 16.5 months, with 7 of 10 responses ongoing at 15 to 28 months.⁵³

A recent study showed the feasibility of combining lenalidomide with rituximab in the setting of indolent lymphoma, and outcomes seemed to be improved without a large increase in toxicity.^{54,55} The combination was evaluated in a small pilot study including 28 evaluable patients with previously untreated, measurable indolent NHL. Patients received up to six 28-day cycles of lenalidomide 20 mg/d on days 1 through 21 and rituximab 375 mg/m² on day 1 of each cycle. The overall response rate was 86% (79% complete response; 7% partial response), and disease was stabilized in 14% of patients. Among patients with FL, 16 of 17 (94%) experienced a complete response. The combination was well tolerated and adverse events were manageable.

A small study by Dutia et al.^{56,57} also showed the efficacy of lenalidomide plus rituximab in patients with relapsed/refractory indolent NHL. Patients (N = 16) had measurable disease and underwent at least one prior therapy. Participants received lenalidomide,

25 mg (amended to 20 mg plus prophylaxis with allopurinol because of tumor lysis syndrome), on days 1 to 21 of a 28-day cycle continued until disease progression. In addition, 4 weekly doses of rituximab were given beginning on day 15 of the first cycle. Rituximab was continued for 4 doses if the patient experienced a partial response or less after first cycle.

Of 16 evaluable patients, 14 patients (75%), 7 of 10 (70%) heavily pretreated patients, and 4 of 7 patients (57%) with rituximab-refractory disease experienced a response, including 85% of patients with FL (38.4% of patients had a complete response). Median progression-free survival for all patients was 12 months. The most frequent grade 3/4 adverse events were fatigue, neutropenia, lymphopenia, and hyponatremia. Thus, this combination seemed to be generally well tolerated and active in this setting and warrants further study.

In patients with CLL, lenalidomide was recently investigated as maintenance treatment,⁵⁸ but the findings are preliminary.

Bortezomib

Bortezomib is a proteasome inhibitor that is indicated for the treatment of patients with multiple my-

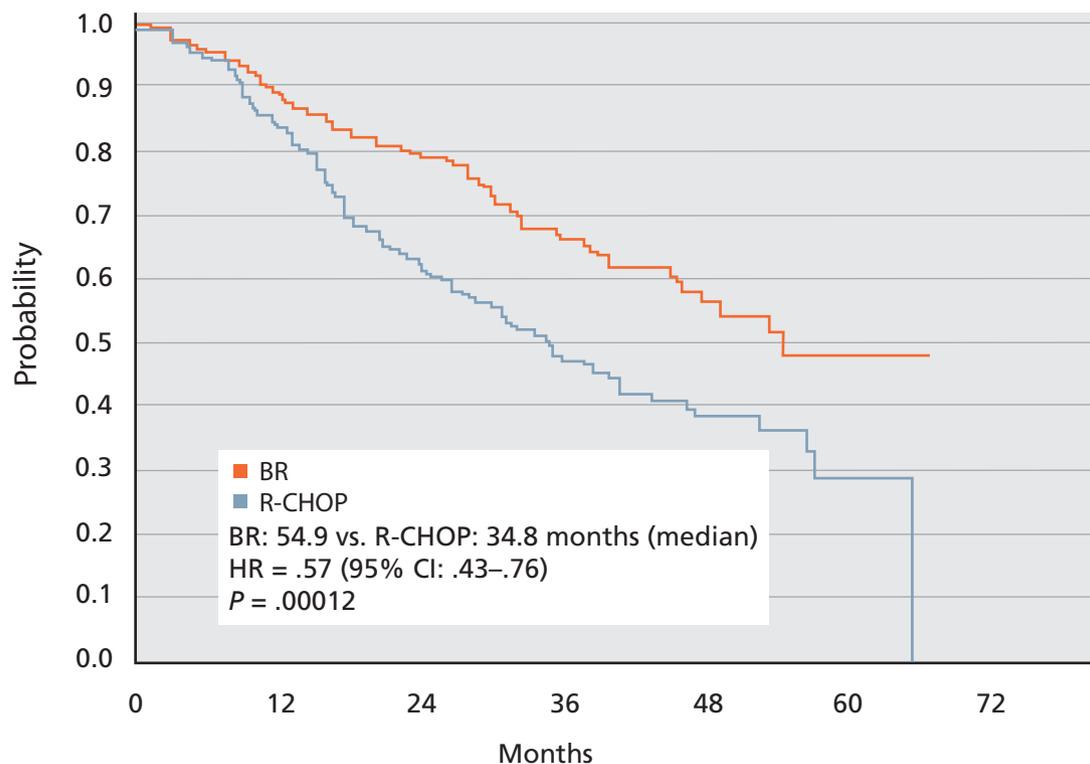


Figure 4. Difference in progression-free survival at a median follow-up of 34 months. BR, bendamustine rituximab; CI, confidence interval; HR, hazard ratio; R-CHOP, rituximab + cyclophosphamide, doxorubicin, vincristine, prednisone.

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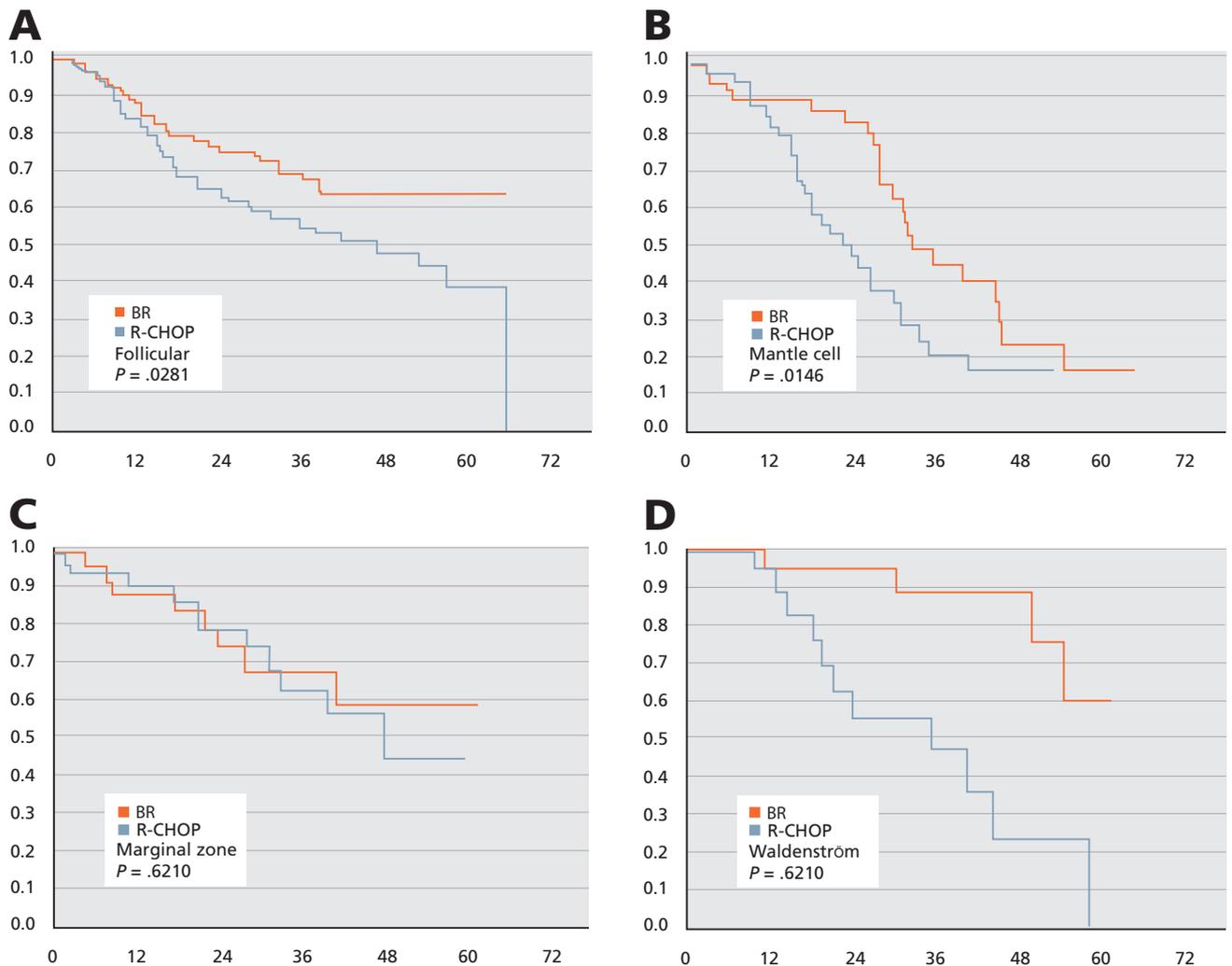


Figure 5. Progression-free survival in lymphoma subgroups. BR, bendamustine rituximab; R-CHOP, rituximab + cyclophosphamide, doxorubicin, vincristine, prednisone

eloma and MCL who have undergone at least one prior therapy. The phase II VERTICAL trial recently showed a benefit for bortezomib, bendamustine, and rituximab (VBR) in patients with relapsed/refractory FL.⁵⁹ Patients had received at least 4 prior doses of rituximab but not bortezomib or bendamustine. Up to five 35-day cycles of VBR were given, consisting of bortezomib, 1.6 mg/m², on days 1, 8, 15, and 22; bendamustine, 90 mg/m², on days 1 and 2; and rituximab, 375 mg/m², on days 1, 8, 15, and 22 during the first cycle and on day 1 of subsequent cycles. Ten patients completed treatment and 29 continued therapy. Of 49 patients assessed after baseline, the overall best response rate was 84% (47% complete response and 37% partial response). VBR was generally well tolerated, with the most frequent treatment-related

toxicities being grade 1 and 2 nausea, fatigue, diarrhea, and vomiting. Grade 3/4 neutropenia, thrombocytopenia, and anemia were reported in 25%, 6%, and 3% of patients, respectively. Thus, this combination warrants further study and may prove beneficial in this setting.

For first-line therapy of WM, rituximab alone or in combination with cyclophosphamide-, bortezomib-, or thalidomide-based regimens can be considered.⁴² Recently, Treon et al.⁶⁰ showed efficacy of bortezomib in previously untreated patients with symptomatic WM when used in combination with dexamethasone and rituximab. Dosing consisted of 4 consecutive cycles of induction therapy with bortezomib, 1.3 mg/m²/d; dexamethasone, 40 mg, on days 1, 4, 8, and 11; and rituximab 375, mg/m², on day 11.

For maintenance therapy, patients received 4 more cycles of the same dosing, each given 3 months apart. The study included 23 patients. As best response, median bone marrow disease involvement declined from 55% to 10% ($P = .0004$), serum IgM levels declined from 4830 to 1115 mg/dL ($P < .0001$), and hematocrit increased from 29.8% to 38.2% ($P = .0002$). The overall response rate was 96%, and at a median follow-up of 22.8 months, 18 of 23 patients remained free of disease progression. The most common toxicity was peripheral neuropathy, which led to discontinuation of treatment in 61% of patients. Herpes zoster infections were also noted, indicating the need for prophylaxis with the bortezomib-dexamethasone-rituximab regimen.

Other Agents

Several novel agents are also being explored in FL in early-stage clinical trials. Hagenbeek et al.⁶¹ studied the anti-CD20 antibody ofatumumab as monotherapy in patients with rituximab-resistant FL. Patients received 8 weekly infusions of ofatumumab, with a first dose of 300 mg, followed by doses 2 through 8 given at 500 or 1000 mg. In this setting of rituximab resistance, ofatumumab had a very low response rate of between 10% and 15%. Thus, at least in this setting, this novel anti-CD20 antibody did not overcome rituximab resistance, which could be explained by the presence of overlapping mechanisms of action and resistance. In a recently reported study of the combination of ofatumumab and CHOP (O-CHOP) in previously untreated patients with FL, O-CHOP achieved high response rates, was effective across all FLIPI risk groups, and was well tolerated.⁶²

Ofatumumab and lumiliximab, an anti-CD23 monoclonal antibody, have both been evaluated in CLL. However, the large phase III randomized trial of lumiliximab plus FCR versus FCR was stopped because the addition of lumiliximab did not improve FCR treatment.⁶³ Ofatumumab was recently approved by the FDA for the treatment of patients with relapsed or refractory CLL, achieving a 50% partial response rate in this setting.

Another anti-CD20 antibody, GA101, a fully humanized and glycoengineered type 2 monoclonal antibody, showed a high response rate and was safe in heavily pretreated patients with indolent NHL.⁶⁴

A recent phase II study evaluated the novel agent, fostamatinib disodium, an oral Syk inhibitor.⁶⁵ A total of 68 patients with recurrent B-cell NHL

were included. The most common adverse events were diarrhea, fatigue, cytopenia, hypertension, and nausea. The response rates ranged from 10% to 55% depending on the type of lymphoma; median progression-free survival was 4.2 months. This activity suggests that this agent warrants further study in patients with FL.

Implications for Clinical Practice and Future Directions

Several new and encouraging advances have been made in the treatment of indolent NHL. Although the watch-and-wait approach still has a role, combined immunochemotherapy remains the standard of care for both first-line and relapsed/refractory disease. As front-line treatment, bendamustine plus rituximab may become a new standard of care, especially for older patients. In contrast, rituximab in combination with chemotherapy followed by rituximab maintenance seems to be the optimal option in patients with relapsed disease.

With regard to the potential benefits of rituximab maintenance therapy after first-line rituximab-containing regimens, the data from the PRIMA study seem to unequivocally support that approach.

Notably, the optimal duration of antibody therapy should be weighed against the adverse effects of long-term use. The SAKK study will establish the optimal duration of maintenance after rituximab monotherapy, whereas the StiL NHL 7-2008 study will identify the duration of rituximab maintenance after bendamustine plus rituximab.

Several studies indicate the benefit of using lenalidomide and bortezomib, especially in combination with rituximab. In addition, several new immunotherapy targets are emerging, and other antibodies, such as those that target vascular endothelial growth factor-mediated signaling, may also warrant evaluation in this setting. Other strategies under evaluation include radioimmunotherapy as initial therapy. It will be important to identify patient subgroups that can optimally benefit from a given treatment approach. Despite these unanswered questions, the current understanding accumulated over recent years has greatly improved long-term outcomes for patients with indolent lymphoma, and guarded optimism is warranted while further advances are anticipated.

Rummel

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