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# R-CHOP, radioimmunotherapy, and maintenance rituximab in untreated follicular lymphoma (SWOG S0801): a single-arm, phase 2, multicentre study

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## Abstract

**Background—**Despite an abundance of therapeutic options, advanced stage follicular lymphoma (FL) remains incurable. Further, the ideal sequence and absolute benefit of post-induction therapy is unclear. SWOG0801 was designed to evaluate consolidative radioimmunotherapy and sequential maintenance rituximab following chemoimmunotherapy.

**Methods—**Eligible patients with treatment naïve advanced stage FL received CHOP for 6 cycles, combined with rituximab during cycles 1–4, followed by iodine-131 tositumomab and subsequent rituximab every 3 months for up to 4 years. The primary endpoint was to estimate the 3-year progression-free survival rate. This final analysis was performed in the intention-to-treat population. Efficacy and safety analyses were done in the intention-to-treat population and the per-protocol population. This trial is registered with ClinicalTrials.gov, number NCT00770224

**Findings—**Between April 1 2009 and December 15 2010, 84 evaluable patients were enrolled and 73 patients completed RCHOP and radioimmunotherapy. The most common ≥3 grade adverse events included neutropenia in 48 patients (57%), leukopenia in 25 patients (40%),

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Authorship

Contributions: The study was designed by the Lymphoma Working Group of the SWOG Cooperative Group; the SWOG Data Center was responsible for central data management; HL and ML performed the analyses of the data. The decision to publish was made by the cooperative group. PMB and HL produced the first version of the manuscript, which was circulated for comments to the other authors.

Declaration of Interests:

thrombocytopenia in 17 patients (20%), and febrile neutropenia in 14 patients (17%). Following induction and RIT, 83 (99%) patients responded including 61 complete responses. Of 69 patients who registered to maintenance therapy, only 41 completed the 4-year treatment secondary to grade 1–2 infections (9) and patient preference (6). After median follow-up of 6·4 years, the progression free survival was 90% (95% CI: 81·9%, 95·1%) at 3 years and 85% (95% CI: 74·8%, 90·7%) at 5 years. The overall survival was 96% (95% CI: 89·3%, 98·8%) and 94% 94% (95% CI: 86·3%, 97·5%) at 3 and 5 years respectively.

**Interpretation—**SWOG S0801 demonstrated near universal responses following chemoimmunotherapy and radioimmunotherapy. However, the majority of discontinuations occurred during maintenance suggesting that rituximab over a 4-year span is not feasible for many patients. Nonetheless, this sequential therapeutic strategy appears to improve outcomes as 94% of pts are without disease progression at 2 years, consistent with the best results ever demonstrated for follicular lymphoma in the National Clinical Trials Network.

### Keywords

follicular lymphoma; radioimmunotherapy; rituximab

## Introduction

Despite the incurability of follicular lymphoma, the median survival of patients has progressively improved with the availability of targeted therapies, approaching two decades in the anti-CD20 era.[1,2] The integration of monoclonal antibodies and radioimmunotherapy as well as phosphoinositide 3-kinase (PI3K) inhibitors and immunomodulatory therapy hold promise in bringing FL closer to a chronic disease for many patients. However, the specific sequence or therapeutic combination to achieve durable disease control for individual patients remains debatable.

These debates are due to opposing viewpoints relating to the treatment of disseminated FL. First, chemoimmunotherapy remains the most commonly utilized initial treatment strategy for patients with FL, given the efficacy of current regimens and general tolerability.[3] Attempting to reduce toxicity, the promise of non-cytotoxic therapy has been limited by the realization that many of the targeted therapies have unique side effects, often having a delayed presentation and becoming more prominent when used in combinations.[4,5] Secondly, radioimmunotherapy remains the most effective single agent available for front line use in FL.[6,7] However, use continues to decrease due to limited availability, concerns about late toxicity and questions regarding integration into current treatment paradigms. Lastly, maintenance rituximab clearly extends remission durations.[8] Nonetheless, its utility remains questioned as rituximab retreatment may provide a similar benefit at a fraction of the cost. [9]

This phase 2 trial was developed to determine if a sequential treatment strategy could further prolong FL disease control. We specifically aimed to evaluate the efficacy and safety when combining two post-induction strategies, RIT consolidation and rituximab maintenance, as each had previously demonstrated improvement in progression free survival (PFS).

## Patients and methods

### Study design and objectives

The primary end point of this multicenter phase 2 study was the 3-year PFS rate in patients with previously untreated follicular lymphoma after administration of RCHOP, iodine-131 tositumomab, and maintenance rituximab. Secondary endpoints included 5-year PFS and overall survival as well as the overall response rate and toxicity. Institutional review boards approved the protocol at each participating site and informed written consent was obtained from all patients before enrollment. All authors had access to the primary clinical trial data. The study was registered before enrolling patients (ClinicalTrials.gov NCT00770224).

### Eligibility Criteria

Patients aged 18 years and older were eligible if they had a diagnosis of stage III, IV or bulky stage II follicular lymphoma, grades 1/2 or 3a, and had not received previous therapy. Central review of pre-treatment biopsies was performed to confirm diagnosis of FL in accordance with WHO 2008 diagnostic criteria. Excisional or core needle biopsies sufficient to show follicular nodal architecture, along with CD20 expression were required. An Eastern Cooperative Oncology Group performance status of 0–2 was required. Baseline laboratory parameters included absolute neutrophil count ≥ 1000 cells/μL, platelet count ≥ 100,000 cells/μL and adequate renal and hepatic function. A cardiac ejection fraction ≥ 45% was required as well. Patients who had other active malignancies, central nervous system lymphoma, HIV positivity, previous solid organ transplantation or other active infection were excluded.

### Protocol Treatment and Clinical Protocol Assessments

Baseline evaluation included history and physical examination, laboratory evaluations, bone marrow biopsy and imaging by computed tomography. All patients were assigned to receiving a 5-year treatment plan consisting of RCHOP, radioimmunotherapy and maintenance rituximab. CHOP was administered every 21 days for up to 6 cycles as published[10] and included rituximab 375 mg/m$^2$ on day 1 of cycles 1–4. Complete blood count and metabolic panel monitoring was performed prior to each cycle. Specific dose modifications for hematologic toxicity, renal dysfunction, hepatotoxicity, neuropathy and other non-hematologic toxicities were included. Patients were subsequently restaged after the sixth cycle with CT and bone marrow biopsy if involved with lymphoma at registration. Patients received iodine-131 tositumomab RIT within 12 weeks following the sixth cycle of CHOP, as previously published.[11] Complete blood counts were monitored weekly. Twelve weeks following RIT, patients were restaged with PET/CT and bone marrow biopsy if previously involved. Stable disease or an objective response was required to be eligible for maintenance therapy. Rituximab 375 mg/m$^2$ was administered every 3 months for up to 4 years. Follow-up evaluations, including CT scans were performed every 6 months during the first 2 years of maintenance therapy and then annually. Adverse events were assessed at baseline, throughout the treatment, and during the 28-day period after treatment discontinuation and were graded by the National Cancer Institute Common Terminology Criteria for Adverse Events Version 4·0. Patients were removed from protocol treatment for progressive disease, unacceptable toxicity, or patient preference.

### Statistical Methods

The primary objective of this trial was to estimate the 3-year progression-free survival rate in patients with advanced stage FL treated with R-CHOP + I-131 tositumomab with rituximab maintenance. Eighty patients was sufficient to estimate the true 3-year PFS within this group to within +/− 0·11. A 3-year PFS of 85% was considered of interest, while further testing was not to be pursued if the true 3-year PFS probability was 70% or lower. This design had a significance level of 5·3% and power of 95%. Secondary endpoints include 5-year PFS, 5-year overall survival, toxicity, and overall response rate.

Progression-free survival was defined as the time from date of registration to date of the first documentation of disease progression or death regardless of cause, whichever occurred first. Patients last known to be alive and progression free were censored at date of last contact. Overall survival was defined as the time from date of registration to date of death as a result of any cause. Patients last known to be alive were censored at date of last contact. Revised International Working Group response criteria were used for classification of objective tumor responses.[12] Patients known to be ineligible or did not receive any protocol treatment were excluded. Point estimates of progression-free survival and overall survival, and their 95% CIs, were estimated using the Kaplan-Meier method. Data as of March 21, 2017 were included in the analysis. This trial is registered with ClinicalTrials.gov, number NCT00770224.

### Role of the funding source

The funding source (National Cancer Institute) had no role in the study design, collection, analysis or interpretation of data, or writing of the report.

GlaxoSmithKline provided Iodine-131 tositumomab and financial support for expenses associated with the cost of nuclear medicine. The corresponding author had full access to all of the data and the final responsibility to submit for publication. All authors had access to the raw data collected in the study.

## Results

### Patient characteristics

Eighty-seven patients were registered between April 1, 2009 and December 15, 2010. Two patients were deemed ineligible because of inability to confirm FL diagnosis on central pathologic review. One additional patient who withdrew consent and received no protocol treatment has been excluded from all analyses. Baseline clinical characteristics for the 84 eligible patients are detailed in Table 1. The median age was 52 years and 44 (52%) patients were female. Sixty-three patients had grade 1–2 disease, 15 patients had grade 3 disease and 2 patients had mixed histology. Grading could not be determined in 4 patients as the only sample provided for central review was bone marrow. Follicular Lymphoma International Prognostic Index (FLIPI) scores were low, intermediate and high in 15 (18%), 34 (40%), and 35 (42%) patients respectively.

### Patient disposition

Seventy-three patients completed RCHOP and RIT as planned. Six patients decided not to proceed to RIT and 3 patients were unable to receive RIT due to prolonged cytopenias and tositumumab unavailability. Two additional patients discontinued induction therapy due to development of unexplained ascites and an unrelated foot puncture wound. Of the 73 patients, 69 registered for maintenance therapy with 3 deciding not to proceed and 1 patient suffering disease progression. Fifty-four patients (78%) completed 2 years and 41 patients (59%) completed 4 years of maintenance therapy. Thirty-five of the 84 patients (42%) required a dose modification of RCHOP and 6 of 69 (9%) patients had a dose modification of maintenance rituximab. The most common reason for discontinuation was infection in 9 patients and patient decision in another 6 cases. Additional reasons for stopping maintenance therapy included protocol non-compliance (3), second malignancy (2), disease progression (1), insurance refusal (1), hepatic dysfunction (1), small bowel perforation (1), joint pain (1), fatigue (1) as well as patient death from cirrhosis in one case and cardiac arrest in another. Of the 28 patients discontinuing during maintenance, 5, 8, 5, and 10 patients stopped in years 1, 2, 3, and 4 respectively.

### Safety

All 84 patients were considered evaluable for toxicity. Treatment-related adverse events are detailed in Table 2 and Table 3. During RCHOP induction and RIT consolidation, myelosuppression accounted for the most common events grade 3 or higher, with neutropenia, thrombocytopenia, and anemia occurring in (48) 57%, (17) 20%, and (6) 7% patients, respectively (Table 2). Febrile neutropenia occurred in 14 (17%) patients and grade 3/4 neuropathy occurred in 7 (8%). During maintenance therapy, the most common grade 3/4 event was lymphopenia, occurring in 4 (6%) patients (Table 3). With a median follow-up of 6·4 years, secondary malignancies have occurred in 7 patients including 2 sarcomas, 2 colorectal carcinomas, 2 acute myelogenous leukemias and 1 case of renal cell carcinoma. The median age at which second malignancies developed was 56 (range 38–65) years and the median time from registration to diagnosis was 5 (range 2.2–8.3) years. Nine patients have died, secondary to unknown etiologies in 3 cases and from cirrhosis and cardiac arrest in 1 case each. Additional potential treatment related causes of death include second malignancies in 4 patients. Despite occurring beyond study follow-up and therefore not counted with the 9 deaths, 1 patient died from progressive multifocal leukoencephalopathy, likely related to treatment.

### Efficacy

Of the 84 eligible patients, 83 underwent formal assessment of response. One patient who discontinued prior to the first response assessment is considered a non-responder. Following RCHOP induction and RIT consolidation the overall response rate was 99% including 61 complete (73%) and 22 partial responses (26%). The overall response rate following maintenance therapy was unchanged at 99% with 2 additional partial responders converting to complete responses.

With a median follow up of 6·4 years (range 5·1–7·7 years), 17 patients have either progressed or died, including the nine deaths detailed above. This resulted in an estimated 3-

year and 5-year progression-free survival of 90% (95% CI: 81·9%, 95·1%) and 85% (95% CI: 74·8%, 90·7%) respectively (Figure 1). Estimates of overall survival at 3 and 5 years were 96% (95% CI: 89·3%, 98·8%) and 94% (95% CI: 86·3%, 97·5%) respectively as well. Patients with a low or intermediate FLIPI score experienced a significantly better progression-free survival compared to high-risk patients (Figure 2).

## Discussion

The results achieved with this sequential treatment regimen, acknowledging the limitations of a single arm phase 2 study, compare very favorably with other first-line strategies evaluating post-induction therapy. RIT consolidation (without a maintenance component) using iodine-131 tositumomab following chemotherapy led to a 76% and 67% PFS at 3 and 5 years respectively in SWOG S0016.[11] Despite trial design differences, this is comparable to results with yttrium-90-ibrutumomab tiuxetan consolidation in the first-line FIT study where the majority of patients did not receive rituximab as part of induction.[13] While iodine-131 tositumomab is no longer available, this data suggests that equivalent results would be expected using ibrutumomab tiuxetan. Similar remission durations were observed with chemoimmunotherapy induction followed by rituximab maintenance as demonstrated by a 75% PFS at 3 years as reported in the PRIMA trial.[14] In the randomized GALLIUM study, anti-CD20 antibodies were compared in patients treated with first-line chemoimmunotherapy and two years of maintenance therapy.[15] Three-year PFS rates of 80% and 73% were demonstrated for the obinutuzumab and rituximab arms respectively. Our sequential strategy potentially builds on these numbers with a provocative 3-year PFS of 90%, including a lower 95% confidence interval of 82%.

However, comparing FL treatment strategies based on solely on PFS has certain limitations. Alternative study designs have allowed clinicians to question the benefit of therapy beyond induction. The RESORT trial demonstrated equivalent disease control for retreatment rituximab when compared to maintenance therapy suggesting that intermittent therapy can provide a similar benefit compared to prolonged rituximab, at least in low tumor burden patients treated with single agent rituximab.[9] In addition, delayed toxicity remains a concern with post-induction therapy. The risk of secondary malignancy has warranted extended follow-up of studies incorporating RIT as first-line therapy. In the current study, 7% of patients developed a second malignancy at 5 years, nearly identical to what had been observed in SWOG S0016.[16] While this rate increased to 14% at 10 years, it was no different compared to long-term results from the FIT trial.[13]

Adding to this concern is the observation that maintenance anti-CD20 antibody therapy adds significant toxicity. Of those who started maintenance therapy in SWOG 0801, only 61% completed the 4-year treatment period mostly due to low grade recurrent infections and concerns regarding the length of therapy. Similar findings were demonstrated by the Swiss Group for Clinical Cancer Research in their comparison of 5 years of rituximab maintenance versus 4 additional infusions following induction therapy.[17] Here, the prolonged schedule was associated with significantly more low-grade adverse events and grade 3 and 4 infections compared to the short-term arm. More worrisome is PML, a life threatening albeit rare side effect resulting from prolonged immunosuppression. Beyond this, additional risks

of lethal side effects have been reported. Despite the short observation period in the GALLIUM study, a 5% fatality rate was reported following bendamustine induction and use of either anti-CD20 antibody, with the majority of the deaths occurring during the maintenance phase.[15] Together, these data suggest that additional therapy following induction warrants a thorough discussion of risks and benefits and that treatment decisions should be made on a case by case basis. Further, maintenance therapy beyond 2 years as well as maintenance of any duration following bendamustine may require further study before routine adoption.

An intriguing finding in our study is the relative lack of early disease progression. Seminal observations from the National Lymphocare Study convincingly show that roughly 20% of patients failing to achieve remission or progressing shortly after first-line chemoimmunotherapy have an inferior 5-year survival.[18] How to subsequently treat these patients remains debatable, with retrospective data supporting approaches from PI3K inhibition to autologous stem cell transplantation.[19,20] Prospective investigations are attempting to address this question, including chimeric antigen receptor T-cell therapy given activity in heavily pretreated refractory patients.[21] In addition, the ongoing SWOG S1608 study will randomize these high-risk patients to CHOP based therapy or newer targeted therapies, attempting to identify the ideal strategy for this population. Despite including over 40% high-risk FLIPI patients, only 6% of patients enrolled to the current study progressed within 2 years, supporting further study of this type of aggressive treatment strategy to prevent early progression.

Limitations to this study include the single arm design precluding definitive comparisons to other upfront treatment strategies. In addition, the patients enrolled were younger than the majority of patients diagnosed with follicular lymphoma. Extrapolating these results to an elderly population may not be possible. Lastly, extended follow-up is needed of any trial incorporating radioimmunotherapy in order to understand the long-term risk of secondary malignancies.

In conclusion, sequential RCHOP, consolidative RIT, and maintenance rituximab produced very favorable outcomes at 5 years but the full treatment plan could not be completed in a substantial portion of patients. As investigations strive to limit treatment durations and develop chemotherapy free treatment regimens, balance must be achieved given the recurrent disease nature. [22] Subsequent steps include defining risk groups at a molecular level and prospective investigations testing risk stratified therapy. These will steer the field toward a precision approach and ultimately enable clinicians to recommend chemoimmunotherapy and post-induction strategies when warranted.

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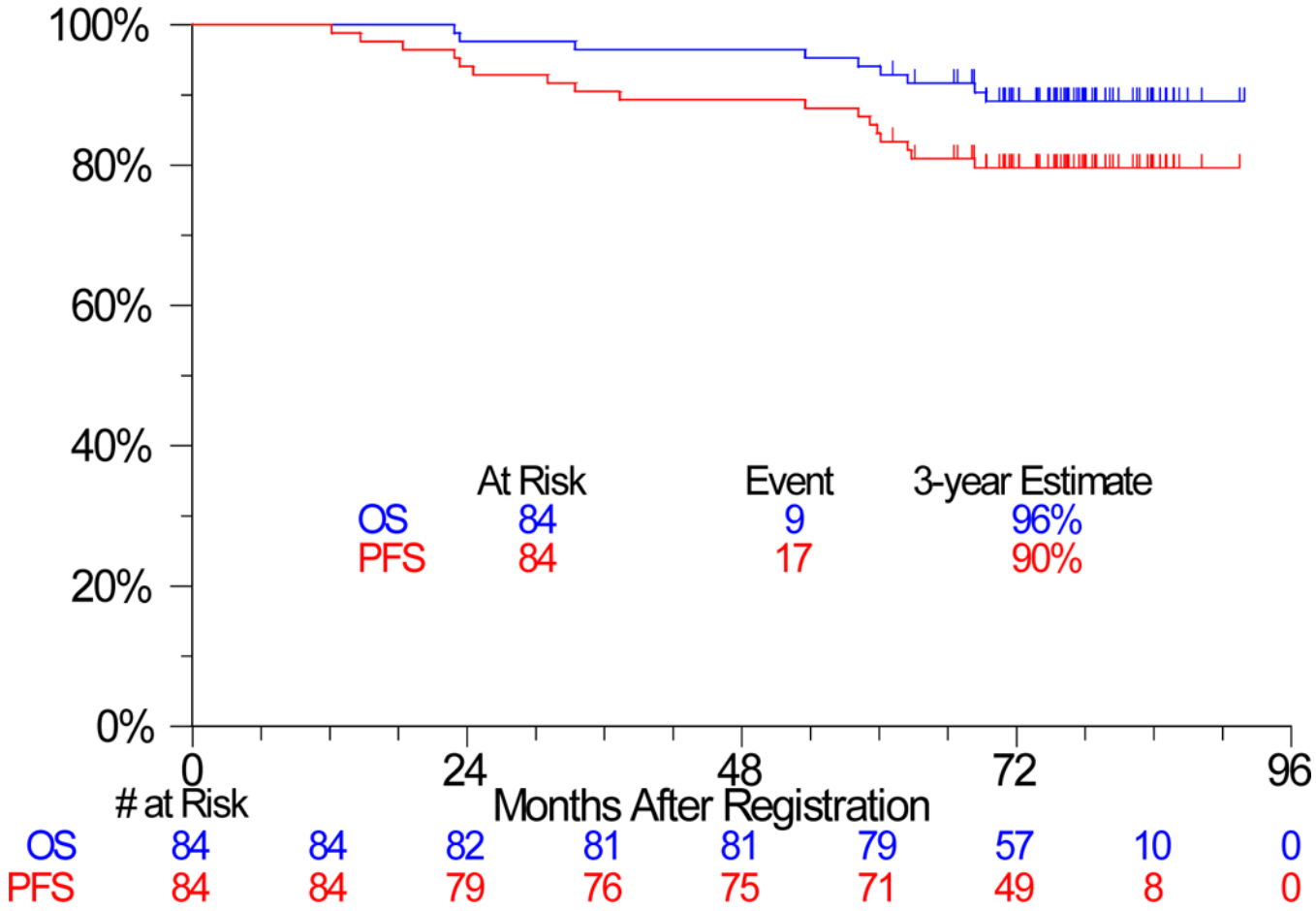


**Figure 1.**
Progression-free survival and overall survival

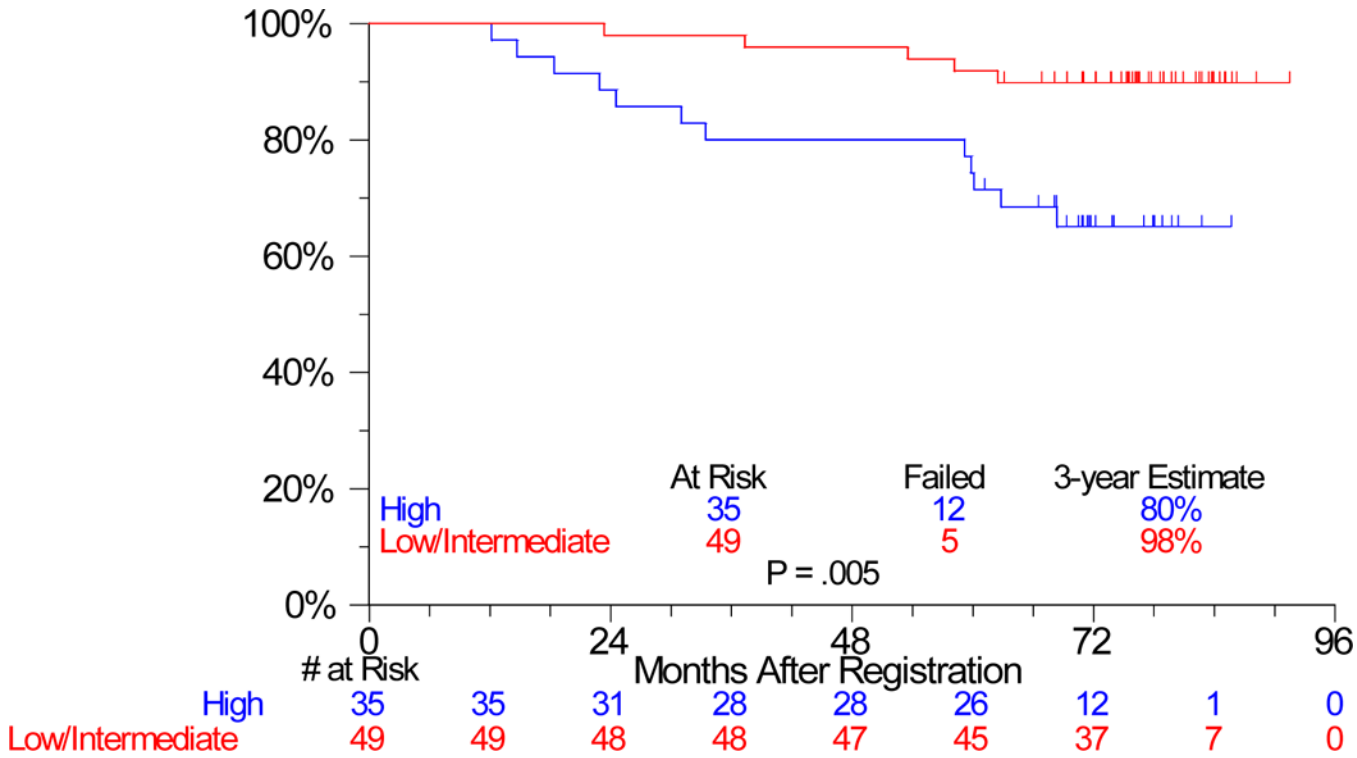


**Figure 2. Progression-free survival stratified by FLIPI risk group.**

High risk (FLIPI score of 3–5); Low/Intermediate risk (FLIPI score of 0–2). FLIPI: follicular lymphoma international prognostic index

**Table 1.**

Patient demographics and baseline clinical characteristics

| Characteristic | N=84 (%) |
|---|---|
| Median age, yr (range) | 52 (29–80) |
| Female | 44 (52) |
| White race | 78 (93) |
| ECOG performance status 0/1 | 52/32 |
| Follicular grade 3 | 15 (18) |
| B symptoms | 20 (24) |
| Disease bulk >10cm | 20 (24) |
| Bone marrow involvement | 52 (62) |
| Elevated LDH | 26 (31) |
| Stage | |
| II | 3 (4) |
| III | 33 (39) |
| IV | 48 (57) |
| FLIPI risk | |
| Low | 15 (18) |
| Medium | 34 (40) |
| High | 35 (42) |

Abbreviations: ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; FLIPI, follicular lymphoma international prognostic index

**Table 2.**

Adverse events occurring during RCHOP and RIT (n=84)

| n (%) | Grade 1–2 | Grade 3 | Grade 4 | Grade 5 |
|---|---|---|---|---|
| Fatigue | 61 (73) | 8 (10) | - | - |
| Nausea | 52 (62) | 3 (4) | - | - |
| Anemia | 50 (60) | 5 (6) | 1 (1) | - |
| Alopecia | 46 (55) | - | - | - |
| Thrombocytopenia | 40 (48) | 9 (11) | 8 (10) | - |
| Sensory neuropathy | 39 (46) | 6 (7) | - | - |
| Constipation | 37 (44) | - | - | - |
| Leukopenia | 26 (31) | 15 (18) | 19 (23) | - |
| Hyperglycemia | 24 (29) | 4 (5) | - | - |
| Anorexia | 23 (27) | 1 (1) | - | - |
| Headache | 20 (24) | 1 (1) | - | - |
| Emesis | 18 (21) | 2 (2) | - | - |
| Insomnia | 16 (19) | - | - | - |
| Taste changes | 16 (19) | - | - | - |
| Generalized weakness | 15 (18) | 1 (1) | - | - |
| ALT increase | 12 (14) | - | - | - |
| Abdominal pain | 12 (14) | 1 (1) | - | - |
| AST increase | 12 (14) | - | - | - |
| Lymphopenia | 11 (13) | 20 (24) | 5 (6) | - |
| Allergic reaction | 11 (13) | 2 (2) | - | - |
| Cough | 11 (13) | 1 (1) | - | - |
| Diarrhea | 11 (13) | 1 (1) | - | - |
| Dyspnea | 11 (13) | 1 (1) | - | - |
| Anxiety | 11 (13) | - | - | - |
| Chills | 11 (13) | - | - | - |
| Muscle pain | 10 (12) | 1 (1) | - | - |
| Mucositis | 10 (12) | - | - | - |
| Bone pain | 9 (11) | 1 (1) | - | - |
| Dizzyness | 9 (11) | - | - | - |
| Neutropenia | 8 (10) | 14 (17) | 34 (40) | - |
| Hypoalbuminemia | 7 (8) | 1 (1) | - | - |
| Urinary tract infection | 6 (7) | 2 (2) | - | - |
| Upper airway infection | 6 (7) | 2 (2) | - | - |
| Weight loss | 5 (6) | 1 (1) | - | - |
| Blurred vision | 5 (6) | 1 (1) | - | - |
| Fever | 4 (5) | 1 (1) | 1 (1) | - |
| Skin infection | 4 (5) | 1 (1) | - | - |
| Sepsis | 2 (2) | 1 (1) | 1 (1) | - |
| Motor neuropathy | 2 (2) | 1 (1) | - | - |

| n (%) | Grade 1–2 | Grade 3 | Grade 4 | Grade 5 |
|---|---|---|---|---|
| Dental infection | 1 (1) | 1 (1) | - | - |
| Pneumonia | 1 (1) | - | 1 (1) | - |
| Febrile neutropenia | - | 12 (14) | 2 (2) | - |
| Wound infection | - | 1 (1) | - | - |
| Heart failure | - | 1 (1) | - | - |
| Opportunistic infection | - | 1 (1) | - | - |
| Syncope | - | 1 (1) | - | - |
| Thrombosis | - | 1 (1) | - | - |

Adverse Events, all grade 3/4, and grade 1/2 occurring in >10% of patients.

**Table 3.**

Adverse events occurring during rituximab maintenance (n=69)

| n (%) | Grade 1–2 | Grade 3 | Grade 4 | Grade 5 |
|---|---|---|---|---|
| Fatigue | 28 (41) | 1 (1) | - | - |
| Thrombocytopenia | 25 (36) | - | - | - |
| Lymphopenia | 23 (33) | 4 (6) | - | - |
| Anemia | 16 (23) | - | - | - |
| Upper airway infection | 13 (16) | 1 (1) | - | - |
| Nausea | 10 (14) | - | - | - |
| Sensory neuropathy | 10 (14) | - | - | - |
| ALT increase | 9 (13) | - | - | - |
| Hyperglycemia | 7 (10) | - | - | - |
| Cough | 7 (10) | 1 (1) | - | - |
| Neutropenia | 6 (9) | 1 (1) | - | - |
| Pain | 5 (7) | 1 (1) | - | - |
| Anxiety | 4 (6) | 1 (1) | - | - |
| Ear infection | 2 (3) | 1 (1) | - | - |
| Generalized weakness | - | 1 (1) | - | - |
| Enteritis | | 1 (1) | - | - |
| Pulmonary hypertension | - | 1 (1) | - | - |
| Cardiomyopathy | - | 1 (1) | - | - |
| Vasovagal episode | - | 1 (1) | - | - |

Adverse Events, all grade 3/4, and grade 1/2 occurring in >10% of patients.