Clinical Cancer Research

# Multicenter, Open-Label, Phase II Study of Bendamustine and Rituximab Followed by 90-Yttrium (Y) Ibritumomab Tiuxetan for Untreated Follicular Lymphoma (Fol-BRITe)

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## Abstract

**Purpose:** Bendamustine and rituximab (BR) has been established as a superior frontline therapy over R-CHOP in the treatment of follicular lymphoma (FL). Yttrium-90 Ibritumomab tiuxetan ($^{90}$YIT) is an effective consolidation strategy after chemotherapy induction. This prospective, single-arm, multicenter, phase II trial evaluated the response rate, progression-free survival (PFS), and tolerability of BR followed by consolidation with $^{90}$YIT in patients with untreated FL.

**Patients and Methods:** The study included grade 1 to 3a FL patients aged ≥18 years, chemotherapy-naïve, and requiring treatment for stage II–IV disease. Study treatment included an initial rituximab treatment, followed by four cycles of BR. Patients were eligible for consolidation with $^{90}$YIT, 6 to 12 weeks after BR, if they obtained at least a partial response after induction had adequate count recovery and bone marrow infiltration < 25%.

**Results:** Thirty-nine patients were treated. Eighty-two percent had an intermediate or high-risk Follicular Lymphoma International Prognostic Index score, and 6 of 39 (15%) were grade 3a. The response rate was 94.8%, and the complete response(CR)/CR unconfirmed (CRu) rate was 77% in the intention-to-treat analysis. The conversion rate from PR to CR/Cru after $^{90}$YIT was 81%. After median follow-up of 45 months, the PFS was 0.71 (95% confidence interval, 0.57–0.89).

**Conclusions:** This report demonstrates that four cycles of BR followed by consolidation with $^{90}$YIT achieve high response rates that are durable. In addition, consolidation with $^{90}$YIT results in a high conversion rate of PR to CR/CRu. A short course of BR followed by $^{90}$YIT is a safe and effective regimen for frontline treatment of FL.

## Introduction

Follicular lymphoma (FL) remains an incurable disease, despite significant advancements in recent decades to treatment and a progressive improvement in median survival. The current goal of treatment is to achieve durable remission while minimizing toxicity and associated complications. The evolution of treatment has seen bendamustine with rituximab (BR) become the preferred regimen over R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone), demonstrating lower incidence of common toxicities, noninferiority in complete response (CR) and overall response rates, and a tendency toward improved progression-free survival (PFS) of disease after 5 years (1–3). The incorporation of novel treatment strategies, including radioimmunotherapy (RIT), continues to improve the outlook for FL patients, leading to remarkable prolongation of remission.

RIT, when used in FL as consolidation after first-line chemotherapy, results in increased CR rate and prolonged PFS when compared with chemotherapy followed by observation (4). Yttrium90 ibritumomab tiuxetan ($^{90}$YIT; Zevalin, Spectrum Pharmaceuticals, Inc.) combines an anti–CD-20 murine monoclonal antibody with the beta-emitting radionuclide 90-yttrium (90Y) by the chelator-linker tiuxetan. The beta emission from Y-90 induces cellular damage by the formation of free radicals in the target and neighboring cells. It has been FDA approved since 2002 for the treatment of relapsed low-grade or follicular B-cell non–Hodgkin lymphoma (NHL), with expanded indications in 2009 to include treatment of newly diagnosed follicular NHL following an initial response to therapy. Several studies have demonstrated the safety and effectiveness of the incorporation of $^{90}$YIT into the treatment regimen of FL patients, particularly those that had not received previous treatment (4–11). The phase III first-line indolent trial of $^{90}$YIT (FIT) in advanced-stage FL in first remission compared observation to consolidation

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## Translational Relevance

Bendamustine and rituximab (BR) is widely accepted as a superior frontline therapy over R-CHOP in the treatment of follicular lymphoma. Yttrium-90 Ibritumomab tiuxetan ($^{90}$YIT) is a targeted monoclonal antibody radioimmunotherapy (RIT) treatment directed against CD20 for B-cell non–Hodgkin lymphoma and an effective consolidation strategy after chemotherapy induction. A previous study has shown prolongation of progression-free survival (PFS) in patients treated with RIT after first remission in advanced follicular lymphoma. We hypothesized that treating follicular lymphoma with a sequentially combined regimen of BR followed by RIT using $^{90}$YIT may improve response rates. In this trial, we demonstrated that this regimen delivered a high response rate [complete response (CR)/complete response unconfirmed (Cru) rate of 77%] and was well tolerated. Furthermore, patients that received BR followed by $^{90}$YIT demonstrated a 45-month PFS of 0.71, a durable PFS compared with previous trial reports. Following $^{90}$YIT, there was a high rate of conversion in partial responders to CR/CRu of 81%, some occurring more than 1 year after treatment.

therapy with $^{90}$YIT in patients with previously untreated advanced FL who achieved partial response (PR) and CR to firstline induction therapy with CVP, CHOP, fludarabine-based regimens, or chlorambucil (4). This trial concluded $^{90}$YIT to be highly effective, delivering a longer time to disease progression with no unanticipated toxicities (4). The PFS in this study was found to be prolonged regardless of PR or CR after first-line therapy. The results also showed that RIT converted 77% of patients from PR to CR/unconfirmed CR (CRu; ref. 4). However, a minority of patients received rituximab so more information was needed to assess its efficacy after rituximab-containing chemotherapy.

Results of several phase II studies have demonstrated that even after rituximab-containing chemotherapy regimens, RIT consolidation results in PR to CR conversions. Furthermore, they found long PFS rates when RIT consolidation was used after a short course of chemotherapy (10, 11). The two trials treated patients with FL with 3 cycles of R-CHOP/R-CVP and 4 weekly doses of rituximab followed by RIT. Using CT assessment of response, the CR/Cru rate of 30% to 40% after chemoimmunotherapy increased to 72% to 82% with RIT. This approach was well tolerated and allowed patients to receive fewer cycles of cytotoxic chemotherapy.

In today's practice, many oncologists consider BR, rather than R-CVP or R-CHOP, to be standard-of-care therapy for untreated FL. The current phase II trial was initiated to determine if a first-line treatment regimen of BR for four cycles, followed by consolidation with $^{90}$YIT, could provide FL patients with a well-tolerated, highly effective therapy.

## Patients and Methods

This multicenter phase II clinical trial was approved by the Dartmouth Institutional Review Board, registered at clinicaltrials.gov as NCT01234766, and complied with the Declaration of Helsinki and the Guidelines for Good Clinical Practice. All patients provided written informed consent and understood that study participation was voluntary. Bendamustine was provided by Teva Pharmaceutical Industries Ltd, and $^{90}$YIT by Spectrum Pharmaceuticals, Inc.

Patients were eligible to be included in this study if they were aged $\geq$18 years with previously untreated, histologically confirmed FL classification grade 1, 2, or 3a, Ann Arbor stages II to IV with either symptomatic or bulky disease (>5 cm), an Eastern Cooperative Oncology Group performance status of <2, and measurable disease with at least one lesion measuring $\geq$2 cm in its greatest transverse diameter. Patients were also required to have adequate renal and hepatic function, and normal organ and marrow function, defined as an absolute neutrophil count (ANC) $\geq$ 1,000/mm$^3$ and platelet count $\geq$ 100,000/mm$^3$. Patients with ANC < 1,000/mm$^3$ and/or platelets < 100,000/mm$^3$ were still considered eligible for study entry if there was >50% bone marrow (BM) involvement with lymphoma. Prior to study enrollment and $^{90}$YIT initiation, female patients of childbearing potential must have had a negative pregnancy test.

### Treatment

Participants received rituximab 375 mg/m$^2$ on day -7, as a lead-in, prior to initiation of cycle 1. For cycle 1, and every subsequent cycle, participants received rituximab 375 mg/m$^2$ on day 1 and bendamustine 90 mg/m$^2$ on days 1 and 2. A cycle was 28 days in duration, and participants were treated for four cycles.

Four to six weeks after completion of the fourth cycle of BR chemotherapy, participants were restaged by physical exam, lab work, CT imaging, BM aspiration, and biopsy. As per study protocol, patients must have completed four cycles of BR, achieved at least a PR using the 1999 Cheson Lymphoma Response Criteria, have an ANC > 1,500/mm$^3$, a platelet count >100,000/mm$^3$, and less than 25% BM involvement with lymphoma prior to the start of consolidation RIT with $^{90}$YIT (12). Participants with stable disease (SD), progression of disease, or those who did not complete four cycles of BR treatment were not eligible to receive RIT.

For eligible patients, RIT treatment was initiated 6 to 12 weeks after the last cycle of BR. $^{90}$YIT was administered in two steps: Step 1 included one infusion of rituximab on day 1. Step 2 was administered on day 8, consisting of a second infusion of rituximab, preceding $^{90}$YIT.

Initially, $^{90}$YIT 0.4 mCi/kg (14.8 MBq/kg) was administered via i.v. infusion over a 10-minute period within 4 hours of completing the rituximab infusion. After 1 patient was unable to receive RIT due to platelets < 150,000/mm$^3$, the protocol was amended to modify the dosage of $^{90}$YIT to 0.3 mCi/kg (11.1 MBq/kg) if platelet counts were within 100,000 to 149,000/mm$^3$ in keeping with the package insert of $^{90}$YIT.

Following RIT, weekly analysis of complete blood count (CBC) with differential was required for a minimum of 12 weeks or until count recovery was documented. Count recovery following RIT was defined as ANC > 1,000/mm$^3$ and platelet count > 100,000/mm$^3$. Use of G-CSF or GM-CSF was permitted in participants who experienced neutropenic fever or neutropenia that persisted beyond 12 weeks after RIT.

Response was additionally assessed with repeat CT imaging 12 weeks after $^{90}$YIT, using the 1999 Cheson Criteria (12). Thereafter, patients were assessed with a CT scan of the neck, chest, abdomen, and pelvis every 6 months for the first 2 years, and then annually.

**Molecular monitoring of minimum residual disease**

Determination of molecular response after BR and after RIT was a preplanned exploratory endpoint. Peripheral blood (PB) and BM were analyzed for the presence of BCL2-IGH translocation, the molecular abnormality commonly observed in FL patients, to assess for minimal residual disease (MRD) during and after treatment. PCR analysis was performed at Dartmouth on blood and BM samples collected from all patients at three time points: baseline, following BR treatment, and then after $^{90}$YIT treatment.

The mononuclear cell fraction was isolated from marrow aspirates by Ficoll–Hypaque sedimentation and cryopreserved for subsequent batch analysis using a double-nested PCR assay to detect the major breakpoint region and the minor cluster region of the BCL2 gene using the method of Gribben and colleagues (13). Patients were considered to have attained a molecular remission if their marrow or PB sample at study entry contained a detectable t (14;18) translocation and became undetectable after protocol treatment.

**Statistical analysis**

The primary objective of this study was to determine the CR and CRu rate after sequential therapy with BR followed by $^{90}$YIT. Secondary objectives included determination of overall response (OR = CR/CRu+PR) rate after a short course (four cycles) of BR; conversion rate from PR to CR following $^{90}$YIT; PFS rate; and safety.

Determination of sample size was based on the historic CR rate of 35%, and thus 35% was considered the null hypothesis (1). The alternative hypothesis was that BR followed by RIT with $^{90}$YIT would increase the CR rate to 55%. It was determined that 39 subjects were required assuming a type I error rate of 5% and power of 80%. The International Response Criteria for non-Hodgkin's Lymphoma was used to assess response (12).

Statistical analysis for the primary endpoint included two preplanned analyses: The first analysis of response rate included only participants who completed all per protocol therapy (4 cycles of BR followed by $^{90}$YIT). The second analysis included all participants who received any portion of study therapy (intention-to-treat analysis) and were assessable for response.

The R package survival (v.2.41.3) was used for stratified OS and PFS analyses. Survival-related data visualization (e.g., Kaplan–Meier plots) was implemented in the R package survminer (v.0.4.2).

## Results

From October 2010 to May 2014, 44 patients were enrolled at the four participating institutions. There were five screen failures, thus, 39 patients (17 men and 22 women) initiated study treatment (Fig. 1). Patient characteristics are shown in Table 1. Median age was 57 years (range, 31–75). The majority of patients had grade 1 or 2 FL, but 15% had grade 3a FL. Ninety percent of subjects had advanced-stage disease including BM involvement in 43.6%. Follicular Lymphoma International Prognostic Index (FLIPI) and FLIPI-2 scores' calculations showed that over 80% had intermediate- or high-risk disease.

Following four cycles of BR, 38 of 39 patients (97.4%) achieved a response with 22 of 39 patients obtaining CR/CRu (56%) and 16 of 39 obtaining PR (41%); the one remaining patient exhibited SD (Fig. 2).

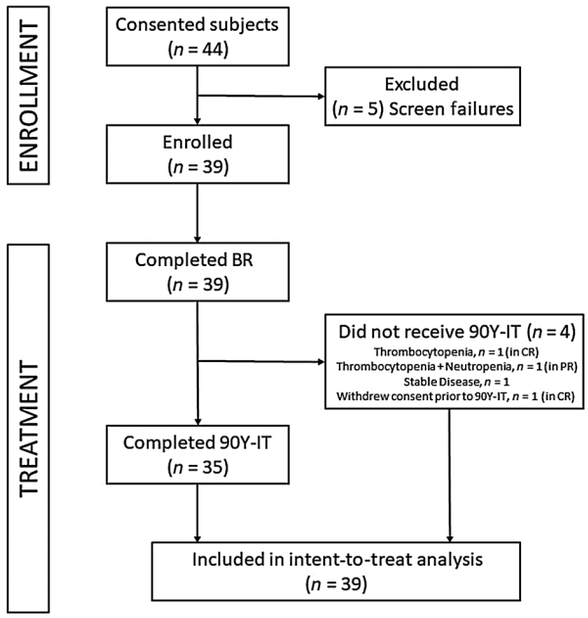


**Figure 1.**
Study CONSORT diagram.

Thirty-five of 39 patients (89.7%) completed treatment with 0.4 mCi/kg $^{90}$YIT. No patient received a reduced dose of $^{90}$YIT. RIT was omitted for the following reasons: one patient was found to have thrombocytopenia of 112,000 per microliter at week 12, occurring prior to protocol amendment allowing RIT to be administered if platelet count >100,000 per microliter; 1 patient had persistent neutropenia and thrombocytopenia; 1 patient had SD and was removed from protocol for radiotherapy; and 1 patient who was in a CR withdrew consent prior to $^{90}$YIT. Thirty-nine patients were included in the intention-to-treat analysis.

**Table 1.** Study patient characteristics

| | **Study group ($n$ = 39)** |
|---|---|
| Age (range) | 57 years (31–75) |
| Sex | |
| Male | 17 (43.6%) |
| Female | 22 (56.4%) |
| Lymphoma grade | |
| 1–2 | 33 (84.6%) |
| 3a | 6 (15.4%) |
| Stage | |
| III | 16 (41%) |
| IV | 19 (49%) |
| BM involvement | |
| Yes | 17 (43.6%) |
| No | 22 (56.4%) |
| FLIPI 1 risk | |
| Low | 7 (17.9%) |
| Medium | 17 (43.6%) |
| High | 15 (38.5%) |
| FLIPI 2 risk | |
| Low | 6 (15.4%) |
| Medium | 27 (69.2%) |
| High | 6 (15.4%) |

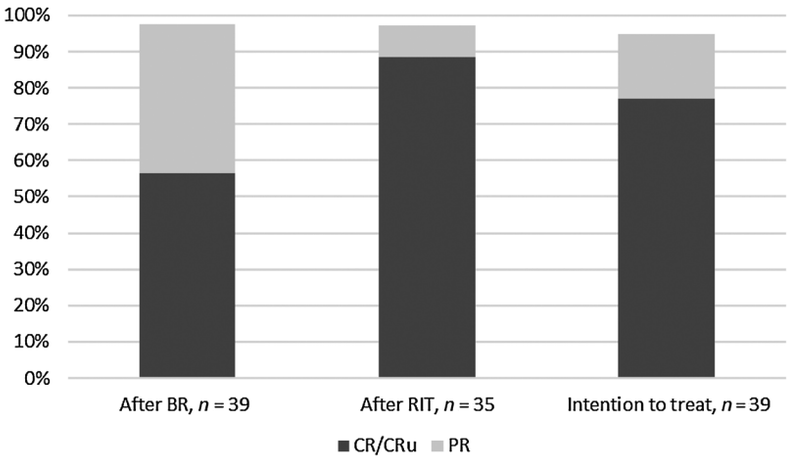


**Figure 2.**
Response rates after sequential therapy.

Following $^{90}$YIT, 31 of 35 patients who received RIT (88.6%) achieved CR/Cru, and 3 sustained a PR (8.6%). The overall response rate (ORR) was 97.1%. One patient (2.8%) who was in a CR/Cru after BR prior to RIT had progression of disease shortly after receiving $^{90}$YIT (Fig. 2). The proportion of patients in PR after BR who reached CR/CRu immediately after $^{90}$YIT was 10 of 16 (62%). Three of 16 (19%) additional patients converted to CR/CRu during follow-up without receiving further treatment, 2 patients at 6 months post $^{90}$YIT, and 1 patient at 16 months post $^{90}$YIT.

Overall, in the intention-to-treat analysis of the entire cohort, 37 of 39 patients (95%) achieved a response, and 30 of 39 patients achieved a CR/CRu (77%) as a best response. One patient with a prior CR after BR had transformation of disease during 90YIT treatment and was counted as a nonresponder in the intention-to-treat analysis. The addition of $^{90}$YIT improved the overall best response (conversion from PR to CR/CRu) in 13 additional patients who initially achieved PR with BR therapy alone, a conversion rate of 81%.

At the median follow-up time of 45 months, the PFS was 0.71 [95% confidence interval (CI), 0.57–0.89; Fig. 3A]. Patients with a PR compared with CR after BR had similar PFS (Fig. 3B). At the median follow-up time of 52 months, OS for all participants was 0.96 (95% CI, 0.87–1.00; Fig. 3A). Three patients experienced transformed disease from FL to diffuse large B-cell lymphoma, at 1.2, 11.2, and 23 months after $^{90}$YIT administration. All were salvaged with a stem cell transplant, two autologous and one allogeneic, and are still alive. Two out of 39 patients died, one due to FL disease progression, and one due to pancreatic cancer, resulting in the 36-month OS of 0.96 (95% CI, 0.87–1.00).

High-risk FLIPI1 was associated with worse PFS, but high-risk FLIPI2 was not significantly different likely due to the low number of patients (Fig. 3C).

### Molecular monitoring and response outcomes

Ten out of 39 patients (26%) had PB detection of BCL2 and 12 (31%) had BM detection of BCL2 by PCR at baseline before any treatment was given, for a concordance rate of 83%. Note that 100% of patients who had detectable BCL2-IGH translocation by PCR at baseline became undetectable for BCL2-IGH translocation after 4 cycles of BR, and remained undetectable after RIT. BCL2-IGH translocation detection at baseline (in either PB or BM) did not affect PFS (data not shown).

### Safety and toxicity

All 39 patients enrolled were assessed for adverse events throughout the study treatment and follow-up period. The BR regimen was well tolerated with grade 3–4 neutropenia noted in 3 of 39 patients and one instance of grade 2 neutropenia, related to either rituximab or bendamustine infusion. During the $^{90}$YIT treatment period, grade 3–4 hematologic toxicities included neutropenia (76%), thrombocytopenia (74%), and anemia (6%). Hematologic effects and duration are noted in Table 2. There were no occurrences of febrile neutropenia or infusion reactions.

During the follow-up period, 1 patient developed JC Virus/Progressive Multifocal Leukoencephalopathy 13 months after receiving the last dose of rituximab and $^{90}$YIT study treatment and is alive in CR, with no further progression of progressive multifocal leukoencephalopathy (PML) after treatment. One patient developed chronic myeloid leukemia 11 months after study treatment and is still alive, and 1 patient developed acute myeloid leukemia at 15 months after study treatment is still alive, which the investigators thought were possibly related to study treatment. No cases of myelodysplasia were reported. One patient developed bladder cancer at 52 months and is still alive, and 1 patient developed pancreatic cancer at 43 months after study treatment had been completed and died 7 months later. An additional patient died due to progression of lymphoma, 35 months after study treatment.

## Discussion

90Y ibritumomab tiuxetan is FDA approved for use as consolidation treatment in patients with follicular NHL who achieved a PR or CR after first-line therapy. This indication is based on results of the FIT trial, which showed significant prolongation of median PFS with the use of RIT consolidation versus observation (4). Several subsequent trials have demonstrated high CR rates and long PFS when RIT consolidation is combined with short courses of chemotherapy, typically 4 rather than 6 cycles of R-CVP/R-CHOP (10, 11). However, bendamustine rituximab is now considered by many to be the optimal first-line therapy for FL based on data demonstrating excellent tolerability and longer PFS from BR compared with R-CHOP (1, 3). Therefore, it is possible that the debulking effect of BR followed by consolidation with RIT may be a safe and even more effective option for patients with FL.

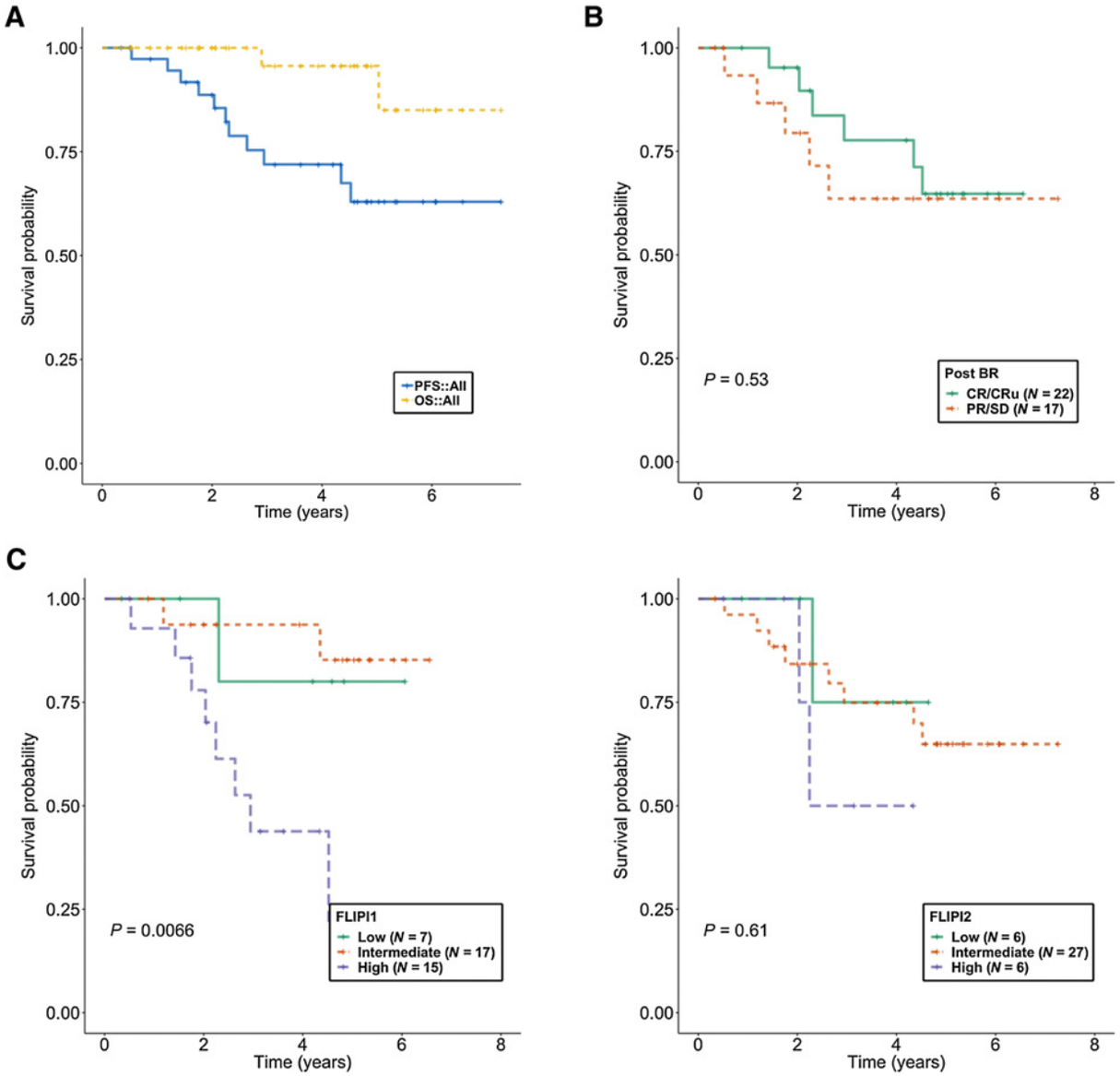


**Figure 3.**

Kaplan–Meier curves. **A**, PFS and OS. **B,** PFS by response status following BR. **C,** Comparison of PFS by FLIPI1 (left) and FLIPI2 (right) status, as well as low-, intermediate-, and high-risk groups.

Although this small phase II trial cannot compare the efficacy of RIT consolidation after R-CHOP or BR, it is the first study to assess tolerability and efficacy of a short course of BR followed by RIT consolidation. In this phase II study of treatment-naïve FL patients, we show that four cycles of a BR regimen, followed sequentially by consolidation with $^{90}$YIT, was well tolerated and resulted in excellent treatment responses, and a durable effect over the follow-up period.

The CR/CRu rate of 77% and long PFS achieved after short course BR followed by $^{90}$YIT is in line with the results reported in prior trials of truncated chemotherapy followed by RIT (10, 11). In our study, we found the conversion rate after RIT to be noteworthy. Sixty-two percent of patients in PR after BR reached CR/CRu immediately after $^{90}$YIT, and an additional 19% converted to CR/CRu with longer follow-up, for a total conversion rate of 81%. Although not previously combined with bendamustine, earlier studies of consolidation therapy with $^{90}$YIT reported similar numbers with 77% of patients in PR after induction chemotherapy converting to CR/Cru after $^{90}$YIT (4). This prior study (4) was criticized because only 14% of patients had received rituximab as part of first-line therapy. However, subsequent trials of R-chemo regimens followed by RIT have shown similar results with conversion rates in the 80th percentile (10, 11). Thus, our trial adds to the data supporting the benefit of RIT consolidation and its ability to increase CR rates even in patients previously exposed to rituximab.

**Table 2.** Hematologic toxic effects following $^{90}$YIT

| | Nadir, median (range) | Days from baseline to nadir, median (range) | Days from nadir to recovery of ANC > 1,000 or platelets > 100, median (range) | Total days from 90YIT to count recovery, median (range) |
|---|---|---|---|---|
| Absolute neutrophil count, $10^9$ cells/L | 0.600 (0–2.800) | 42 (14–85) | 8 (3–36) | 52 (14–97) |
| Platelets, $10^9$ cells/L | 21 (4–126) | 34 (25–97) | 28 (7–217) | 63 (27–252) |
| Hemoglobin, g/dL | 10.2 (6.7–13.8) | 56 (6–167) | n/a | n/a |

The shortened course of BR used in this trial resulted in a very high ORR of 97% with 56% patients obtaining CR/Cru. This CR rate compares very well to the BRIGHT and StiL studies, which showed CR of 31% and 40%, respectively (1, 3). We would expect similar outcomes as patient age, stage, and FLIPI score in those trials were generally similar to our study, and all three trials assessed response with CT scan imaging. However, the StiL and Bright trials included all indolent lymphoma subtypes and thus only 55% and 69%, respectively, of their patient population had FL. So, although the small size of our population and lack of independent central review of responses may have resulted in a falsely high CR rate in our study, it is possible that our results may be an accurate demonstration of the sensitivity of FL to BR. In fact, there are multiple phase II trials of BR in FL patients that have shown CR rates of 48% to 61%, similar to our findings (14–16).

The main toxicity associated with $^{90}$YIT after BR is myelosuppression for which the median recovery time was 7 weeks to reach ANC >1,000, and 9 weeks to reach platelets over 100, comparable with other RIT studies (10, 11, 17–20). The rate of hematologic malignancies in this study was 5.1%, including one acute myeloid leukemia (AML) and one chronic myeloid leukemia (CML), which is similar to the 8-year actuarial risk of MDS or AML of 4.2% in the $^{90}$YIT group in the FIT trial (21). However, the median follow-up in the FiT trial was 75 months versus 52 months in our trial, so it is possible that we may see an increasing number of secondary hematologic malignancies with longer follow-up. Furthermore, the small sample size of our study and lack of a comparator arm make it difficult to truly assess whether there is an increased risk of secondary malignancy with the addition of RIT to short course BR. Larger studies and meta-analyses are needed to determine the contribution, if any, of RIT to secondary malignancies, because lymphoma, chemotherapy, and immune suppression can also contribute to secondary malignancies.

We investigated the ability of short course BR + RIT consolidation to lead to molecular response as determined by clearance of BCL2 translocation from blood and BM. All 39 patients were tested at baseline, but only 12 (31%) were positive for BCL2 gene rearrangement. This is a much lower rate of BCL2 positivity than the 62% to 68% reported in the literature (21–23). Although 100% of patients who had detectable BCL2 by PCR at baseline became undetectable for BCL2-IGH translocation after 4 cycles of BR, and remained undetectable after RIT, the sensitivity of our assay may not be able to detect a true MRD state. The PCR assay used to detect the BCL-2 translocation was described by Gribben and colleagues (13) and validated for clinical use in our clinical genomics laboratory. Although our detection rate was lower than that reported by Gribben and colleagues, these assays are not known to detect more than 70% of the translocation sites in FL cases. These results point out a need for a sensitive MRD assay such as deep sequencing.

Another limitation of this study was the single-arm design which does not provide definitive comparisons with other upfront treatment strategies for FL patients, such as maintenance rituximab. Maintenance rituximab, or even the newer anti-CD20 antibody, obinutuzumab, is not without limitations, however. As has been recently reported, there is considerable infectious risk including death from serious infections with prolonged maintenance over 2 years (24). This makes a shorter course of RIT appealing. A randomized trial comparing $^{90}$YIT versus maintenance immunotherapy after induction chemoimmunotherapy is required to compare the durability of response and assess infectious risk and long-term toxicities from the treatment.

In conclusion, in this clinical investigation of untreated FL patients who received a short course of BR followed by consolidation with $^{90}$YIT, we demonstrate this regimen was well-tolerated with high response rates, high conversion rates to CR/CRu, with the expected hematologic side effects profile of chemoimmunotherapy and radiotherapy. This is the first data of sequencing RIT after bendamustine and rituximab, and can be considered an option for treatment for those patients and providers seeking a shorter and finite treatment duration.

## Disclosure of Potential Conflicts of Interest

C.A. Costa reports receiving speakers bureau honoraria from Celgene. S.P. Yen is a consultant/advisory board member for AbbVie. A.W. Beaven reports receiving speakers bureau honoraria from Celgene and Spectrum. No potential conflicts of interest were disclosed by the other authors.

## Authors' Contributions

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**Writing, review, and/or revision of the manuscript:** F. Lansigan, C.A. Costa, E.S. Winer, D. Findley, Y. Chen, A.W. Beaven
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**Study supervision:** F. Lansigan
**Other (research nurse):** L. Shaw

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