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# Comparison of the effectiveness of frontline chemoimmunotherapy regimens for follicular lymphoma used in the United States

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**Abstract**

**To compare the effectiveness of frontline rituximab-chemotherapy regimens in clinical practice, we examined outcomes for patients with low-grade, stage III/IV follicular lymphoma receiving rituximab (R) with cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP), R with cyclophosphamide, vincristine and prednisone (R-CVP) or R with a fludarabine-based regimen (R-Flu) as frontline therapy. In total, 611 patients meeting these criteria were identified in the National LymphoCare Study: 47% receiving R-CHOP ($n = 287$), 31% receiving R-CVP ($n = 187$) and 22% receiving R-Flu ($n = 137$). Overall response rates were high (R-CVP 87%, R-CHOP 93%, R-Flu 94%; $p = 0.017$). Median follow-up was 7.4 years. R-CVP was associated with lower 5-year overall survival (R-CVP 76%, R-CHOP 86%, R-Flu 86%; $p = 0.021$) and progression-free survival (R-CVP 49%, R-CHOP 58%, R-Flu 64%; $p = 0.029$). There were no significant differences in survival in Cox models adjusted for baseline clinical factors, practice region/setting and post-treatment R maintenance/observation.**

**Keywords:** Follicular lymphoma, frontline, outcomes, rituximab, chemotherapy

## Introduction

Follicular lymphoma (FL) is the most common indolent lymphoma in the United States and Western Europe [1,2], with a disease course characterized by high initial response rates to chemotherapy followed by eventual relapse and progressive disease. The majority of patients with FL present with advanced disease and are considered incurable with standard therapy, which has led to marked variability among clinicians in their goals and strategies for treatment [3,4]. Overall survival (OS) for FL has improved over time, and choice of initial therapy may impact outcomes [5–7].

Despite published data suggesting that bendamustine plus rituximab (BR) is a preferred first-line treatment approach [8], there is no universal consensus on the initial management of FL [9], as was illustrated by the initial publication of the National LymphoCare Study (NLCS) [4]. Of the initial management strategies used in patients with FL diagnosed in the USA between 2004 and 2007, over 50% of patients received rituximab (R) with chemotherapy, with preferred regimens emerging as R plus cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP); R plus cyclophosphamide, vincristine and prednisone (R-CVP); or R plus a fludarabine-based regimen (R-Flu). Moreover, there are limited data comparing the effectiveness of frontline R-based chemotherapy combinations, particularly in the community clinical practice setting. The purpose of this study was to examine factors that were associated with the initial management strategy selected by clinicians and to compare the effectiveness and safety of R-CVP, R-CHOP and R-Flu as first-line therapy for patients with advanced-stage FL treated in US practices.

## Methods

The NLCS is a prospective, multicenter, observational study that enrolled over 2700 previously untreated patients with FL diagnosed between 2004 and 2007 at 265 sites in the USA, as previously described [4]. Written informed consent was obtained from individual patients before participation, and the protocol was approved by each site's institutional review board. This study was conducted in accordance with the Declaration of Helsinki. Eligible patients for this study were adults (≥ 18 years of age) diagnosed with FL within 6 months of enrollment, without prior history of lymphoma. There was no central pathology review; the local pathology

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report defined FL diagnosis [4]. Our analysis was further restricted to patients with stage III/IV disease, histological grade 1/2, who had received frontline R plus chemotherapy. Patients who progressed before receiving treatment were excluded. Initial and subsequent management decisions were made by the treating physician without protocol-specified treatment assignments or recommendations, including the indication to initiate therapy. This analysis was not restricted to patients with high tumor burden, as this metric was not captured as a data element [10]. Assessment of response was made by the treating physician and reported quarterly.

NLCS data management and analysis are guided by an advisory board composed of academic and community investigators as well as a patient advocate. The advisory board participated in all phases of the study, met quarterly, retained full access to data listings and collaborated with the primary author (L.J.N.) and the sponsor regarding interpretation and publication of the data. This manuscript was written *de novo* by L.J.N. and members of the advisory board following approval of a protocol with prespecified endpoints, hypotheses and plans for analysis. OS was the primary measure of effectiveness and was defined as the number of days from diagnosis up to and including the date of death from any cause. Secondary measures of effectiveness were progression-free survival (PFS), defined as the number of days from the date of diagnosis up to and including the date of disease progression (as assessed by the treating physician), or death from any cause, and transformation-free survival (TFS), defined as the number of days from the date of diagnosis up to and including the date of first suspected or confirmed transformation, as assessed by the treating physician, or death from any cause. Patients who had not yet experienced an event at the time of analysis were censored at the date of the most recent response assessment (for PFS and TFS) or last contact date (for OS).

Descriptive statistics for baseline characteristics and usage of maintenance R were compared using analysis of variance and Pearson $\chi^2$ tests. Defining R maintenance use was similar to previously published reports [11]. We employed a generalized logistic model using backward selection with a significance level of 0.05 to identify baseline factors of clinical interest that were associated with treatment selection. Kaplan–Meier estimation was used to evaluate OS, PFS and TFS for the three groups along with the log-rank test (unadjusted results). To evaluate the effects of treatment on OS and PFS, we used Cox proportional hazards models, adjusting for baseline factors (sex, age [$\leq$ 50, 51–60, 61–70 and $>$ 70 years], number of nodal sites, bone marrow involvement, lactate dehydrogenase, hemoglobin, geographic region, practice setting) and use of maintenance R following treatment, a time-dependent covariate (adjusted results). Additional sensitivity analyses were performed using propensity scores, adjusting for baseline imbalances between treatment groups [12]. Cox proportional hazards models with a robust estimate of treatment variance and adjustment for post-induction treatment (R maintenance or observation) were fitted to patients matched by treatment propensity scores.

## Results

Of more than 2700 patients enrolled in NLCS, 611 patients met the criteria of having low-grade, stage III/IV FL and receipt of one of the frontline regimens of interest. Within this cohort, 47% received R-CHOP ($n = 287$), 31% received R-CVP ($n = 187$) and the remaining 22% received R-Flu ($n = 137$). The R-Flu-based regimens included R plus fludarabine, mitoxantrone and dexamethasone (R-FND; $n = 43$ [31%]); R plus fludarabine and cyclophosphamide (R-FC; $n = 35$ [26%]); and R plus fludarabine and mitoxantrone (R-FM; $n = 22$ [16%]), with the remaining cases involving some other R plus fludarabine combination ($n = 37$ [27%]). The baseline characteristics of patients included in each treatment group are shown in Table I. There were significant differences across treatment categories by age, sex, geographic region, center type and usage of R maintenance. The median age was 56 years in the R-CHOP group (range 22–84), 62 years in the R-CVP group (39–89) and 58 years in the R-Flu group (32–84); $p < 0.0001$; 31% of patients in the R-CVP group were over the age of 70 years, compared with 12% in the R-CHOP and 23% in the R-Flu groups. A higher percentage of patients in the R-CHOP group were male compared with the R-CVP and R-Flu groups (56% vs. 43% and 40%, respectively, $p = 0.002$). The majority of patients who received R-CVP also received R maintenance (61%) compared with 46% of R-CHOP and 51% of R-Flu treated patients ($p = 0.027$). There was a higher percentage of patients with high-risk Follicular Lymphoma International Prognostic Index (FLIPI) score (defined as poor; 3–5) in the R-CVP group (58%) compared with R-CHOP (47%) and R-Flu (43%); $p = 0.086$. Additional baseline characteristics that were not significantly different between the three groups included Eastern Cooperative Oncology Group performance status (ECOG PS), stage, nodal sites, extranodal sites, serum lactate dehydrogenase, hemoglobin, presence of B symptoms, bone marrow involvement and race.

Factors associated with treatment selection from the generalized logistic model are shown in Table II. Patients $>$ 70 years had a lower likelihood of receiving R-CHOP (odds ratio [OR] 0.23 relative to patients $\leq$ 50 years, 95% confidence interval [CI] 0.13–0.42, $p < 0.0001$). Female patients were less likely to receive R-CHOP than R-CVP (OR 0.54, 95% CI 0.36–0.80, $p = 0.001$). There were also differences in treatment patterns across the USA, as we previously described [4]; patients in the Northeast were less likely to receive R-CHOP than R-CVP (OR 0.47 relative to the Midwest, 95% CI 0.24–0.89, $p = 0.002$). Race, hemoglobin, nodal sites, lactate dehydrogenase, FLIPI risk category and bone marrow involvement were not significantly associated with the treatment administered, and were removed in the backward selection of the generalized logit model.

A significantly higher percentage of patients treated with R-CHOP (92%) and R-CVP (86%) completed planned therapy compared with R-Flu (81%); $p = 0.005$. Discontinuation due to toxicity was more frequent with R-Flu, with 12% of all patients treated with R-Flu discontinuing due to toxicity (vs. 4% R-CHOP and 8% R-CVP, $p = 0.01$).

Table III compares outcomes by initial treatment regimen for patients with low-grade, advanced-stage FL and for those

Table I. Patient baseline characteristics by frontline treatment.

| Characteristic | R-CHOP ($n = 287$) | R-CVP ($n = 187$) | R-Flu ($n = 137$) |
|---|---|---|---|
| Age*, median years (range) | 56 (22–84) | 62 (39–89) | 58 (32–84) |
| Age group, *n* (%) | | | |
| ≤ 50 years | 100 (35) | 43 (23) | 37 (27) |
| 51–60 years | 89 (31) | 39 (21) | 48 (35) |
| 61–70 years | 65 (23) | 48 (26) | 21 (15) |
| > 70 years | 33 (12) | 57 (31) | 31 (23) |
| Male*, *n* (%) | 160 (56) | 80 (43) | 55 (40) |
| ECOG PS, *n* (%) | | | |
| 0 | 127 (61) | 77 (56) | 63 (72) |
| 1 | 71 (34) | 50 (37) | 23 (26) |
| ≥ 2 | 12 (6) | 10 (7) | 2 (2) |
| Missing | 77 | 50 | 49 |
| FLIPI risk (score), *n* (%) | | | |
| Good (0–1) | 43 (18) | 22 (14) | 17 (16) |
| Intermediate (2) | 87 (36) | 46 (28) | 44 (42) |
| Poor (3–5) | 114 (47) | 94 (58) | 45 (43) |
| Missing | 43 | 25 | 31 |
| B symptoms, *n* (%) | | | |
| Yes | 118 (41) | 71 (38) | 42 (31) |
| Stage, *n* (%) | | | |
| III | 107 (37) | 68 (36) | 55 (40) |
| IV | 180 (63) | 119 (64) | 82 (60) |
| Nodal sites, *n* (%) | | | |
| ≥ 5 | 146 (53) | 102 (56) | 62 (47) |
| Missing | 10 | 5 | 6 |
| Extranodal sites, *n* (%) | | | |
| ≥ 2 | 104 (37) | 59 (33) | 40 (30) |
| Missing | 8 | 6 | 3 |
| LDH, *n* (%) | | | |
| > ULN | 70 (30) | 37 (25) | 20 (19) |
| Missing | 53 | 36 | 31 |
| Hb, *n* (%) | | | |
| < 12 g/dL | 66 (24) | 47 (26) | 36 (27) |
| Missing | 14 | 8 | 5 |
| Bone marrow involvement, *n* (%) | | | |
| Yes | 135 (57) | 92 (61) | 70 (65) |
| Missing | 48 | 35 | 29 |
| Geographic region*, *n* (%) | | | |
| Midwest | 96 (33) | 66 (35) | 47 (34) |
| Northeast | 24 (8) | 31 (17) | 13 (10) |
| Southeast | 95 (33) | 54 (29) | 53 (39) |
| Southwest | 23 (8) | 14 (8) | 16 (12) |
| West | 49 (17) | 22 (12) | 8 (6) |
| Center type*, *n* (%) | | | |
| Community | 218 (76) | 152 (81) | 118 (86) |
| Follow-on treatment*, *n* (%) | | | |
| R-maintenance | 105 (46) | 79 (61) | 47 (51) |
| Not classified† | 59 | 57 | 44 |

ECOG PS, Eastern Cooperative Oncology Group performance status; FLIPI, Follicular Lymphoma International Prognostic Index; LDH, lactate dehydrogenase; ULN, upper limit of normal; Hb, hemoglobin; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; R-CVP, rituximab, cyclophosphamide, vincristine and prednisone; R-Flu, rituximab and a fludarabine-based regimen.

*Pearson $\chi^2$ *p*-value < 0.05.

†Patients who had a valid response assessment and did not progress or receive second-line treatment within 215 days of completing initial treatment were classified to either "R-maintenance" if rituximab maintenance was initiated during this period or "observation" if it was not. Patients not meeting either criterion were not classified.

with high-risk FLIPI. The clinician-reported overall response rates (ORRs) for patients treated with R-CVP, R-CHOP and R-Flu were 87%, 93% and 95%, respectively ($p = 0.02$). With a median follow-up of 7.4 years, the median OS had not been reached (R-CVP 54 events, R-CHOP 54 events, R-Flu 26 events). Significant differences were seen in 5-year OS (R-CVP 76%, R-CHOP 86% and R-Flu 86%, $p = 0.021$; Figure 1) and PFS estimates (R-CVP 49%, R-CHOP 58% and R-Flu 64%, $p = 0.029$; Figure 2), with both showing inferior outcomes in patients treated with R-CVP. Similarly, significant differences in 8-year OS estimates were seen, 65% for patients in the R-CVP group, 79% in the R-CHOP group and 79% for patients in the R-Flu group ($p = 0.012$; Figure 1). The median PFS was 4.8 years in the R-CVP group (101 events), 6.4 years in the R-CHOP group (138 events) and had not been reached in the R-Flu group (57 events; Table III). Eight-year PFS estimates were inferior in the R-CVP group (R-CVP 34%, R-CHOP 42%, R-Flu 53%, $p = 0.020$; Figure 2). The median TFS had not been reached in any group. Five-year TFS estimates were 65% in the R-CVP group, 77% in the R-CHOP group and 73% in the R-Flu group ($p = 0.039$) (8-year TFS: R-CVP 55%, R-CHOP 69%, R-Flu 66%, $p = 0.057$; Figure 3).

Table IV shows PFS and OS results for patients with low-grade, advanced-stage FL after adjusting for FLIPI risk components and other factors (sex, bone marrow involvement, practice setting [academic/community], geographic

Table II. Patient characteristics associated with selection of frontline treatment.

| Characteristic* | R-CHOP vs. R-CVP, OR (95% CI) | R-Flu vs. R-CVP, OR (95% CI) |
|---|---|---|
| Age, years | | |
| 51–60 vs. ≤ 50 | 1.01 (0.59–1.72) | 1.57 (0.84–2.94) |
| 61–70 vs. ≤ 50 | 0.58 (0.34–0.99) | 0.55 (0.28–1.11) |
| > 70 vs. ≤ 50 | 0.23 (0.13–0.42) | 0.64 (0.34–1.22) |
| Sex | | |
| Female vs. male | 0.54 (0.36–0.80) | 1.04 (0.66–1.65) |
| ECOG PS† | | |
| ≥ 1 vs. 0 | 0.99 (0.62–1.58) | 0.57 (0.31–1.02) |
| Geographic region | | |
| Northeast vs. Midwest | 0.47 (0.24–0.89) | 0.62 (0.29–1.33) |
| Southeast vs. Midwest | 1.43 (0.88–2.32) | 1.60 (0.92–2.78) |
| Southwest vs. Midwest | 1.17 (0.54–2.52) | 1.49 (0.65–3.41) |
| West vs. Midwest | 1.73 (0.92–3.23) | 0.49 (0.20–1.23) |
| Practice setting | | |
| Academic vs. community | 1.57 (0.96–2.58) | 0.72 (0.38–1.37) |

ECOG PS, Eastern Cooperative Oncology Group performance status; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; R-CVP, rituximab, cyclophosphamide, vincristine and prednisone; OR, odds ratio; CI, confidence interval; R-Flu, rituximab and a fludarabine-based regimen.
*Lactate dehydrogenase level, number of nodal sites, bone marrow involvement, overall Follicular Lymphoma International Prognostic Index score, hemoglobin level and race/ethnicity were not significantly different between treatment groups ($p > 0.05$) and were removed in the backward selection of the generalized logit model.
†Owing to a large amount of missing data, missing values were treated as a separate group.

region and observation/maintenance R) in multiple variable Cox proportional hazards models. R-Flu was associated with significantly longer PFS compared with R-CVP (hazard ratio [HR] 0.69, 95% CI 0.49–0.97). There was no significant difference in OS (R-CHOP vs. R-CVP: HR 0.83, 95% CI 0.55–1.25; R-Flu vs. R-CVP: HR 0.72, 95% CI 0.44–1.17), possibly due to too low a power to show a significant OS difference (21% power to show a difference between R-CHOP and R-CVP if the true HR is 0.80 and 32% power to show a difference between R-Flu and R-CVP if the true HR is 0.70). Propensity score-adjusted estimates of PFS and OS by frontline treatment are presented in Table V. In these analyses, 150 matched pairs of patients receiving R-CVP and R-CHOP were compared as well as 107 R-Flu and R-CVP matched pairs. Effects similar to those seen in adjusted Cox regression analyses were observed in these models.

Eighty-nine patients developed a new secondary malignancy while enrolled in this study: 27 patients (14%) in the R-CVP group, 38 patients (13%) in the R-CHOP group and 24 patients (18%) in the R-Flu group. Table VI shows the various second malignancies in each group. Four patients (3%) in the R-Flu group, three patients (2%) in the R-CVP group and three patients (1%) in the R-CHOP group were diagnosed with myelodysplastic syndrome (MDS). Two patients (0.7%) in the R-CHOP group, one patient (0.5%) in the R-CVP group and one patient (0.7%) in the R-Flu group were diagnosed with leukemia.

## Discussion

Although chemoimmunotherapy is most often the initial management strategy for FL in the USA [4], great debate remains regarding the preferred frontline regimen. This is the first large, prospective, observational study across community and academic sites to examine factors that influence selection of frontline therapy and compare the effectiveness of the three most common frontline regimens prescribed for advanced-stage FL in the USA. Adjusted estimates of OS suggest comparable outcomes among the commonly prescribed regimens, despite the apparent association of R-Flu with superior PFS and both R-CHOP and R-Flu appearing to have superior 5- and 8-year OS estimates compared with R-CVP. The findings of superiority for R-CHOP and R-Flu compared with R-CVP in unadjusted 5-year OS, and a failure to observe a significant difference between these groups in adjusted and propensity score-matched Cox regression models for OS, may arise because of differences in the baseline characteristics between these groups. Patients treated with R-CVP were older and more commonly had high-risk FL. The lack of significant differences in adjusted OS may also be accounted for by low power, and suggests that longer follow-up and/or observational studies with larger numbers of patients are needed. Nevertheless, these findings lend insight into the "real-world effectiveness" of the various management strategies available in clinical practice, and aid in discussions of expected outcomes of commonly prescribed regimens for previously untreated patients with advanced-stage FL.

As with any observational study, the main impediment to the validity of our study is selection bias, in which both measured and unmeasured variables can confound treatment selection and the outcomes of interest. Recognizing these threats, the NLCS and these analyses have been conducted in accordance with established guidelines for performing comparative effectiveness research [13–15]. For example, a formal study protocol including a data-analysis plan was submitted prior to the design and execution of this study, and a propensity score analysis that addressed bias by matching patients across treatment assignments based on

Table III. ORR and outcomes for all patients and for patients with high-risk FLIPI by frontline treatment.

| | All patients | | | High risk (FLIPI 3–5) | | |
|---|---|---|---|---|---|---|
| | R-CHOP ($n = 287$) | R-CVP ($n = 187$) | R-Flu ($n = 137$) | R-CHOP ($n = 114$) | R-CVP ($n = 94$) | R-Flu ($n = 45$) |
| ORR, % | 93 | 87 | 95 | 94 | 85 | 95 |
| Median OS | NR | NR | NR | NR | NR | NR |
| 5-year OS, % | 86 | 76 | 86 | 76 | 65 | 70 |
| 8-year OS, % | 79 | 65 | 79 | 62 | 51 | 57 |
| Median PFS, years | 6.4 | 4.8 | NR | 4.0 | 3.8 | 5.9 |
| 5-year PFS, % | 58 | 49 | 64 | 45 | 38 | 52 |
| 8-year PFS, % | 42 | 34 | 53 | 30 | 23 | 36 |

FLIPI, Follicular Lymphoma International Prognostic Index; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; NR, not reached; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; R-CVP, rituximab, cyclophosphamide, vincristine and prednisone; R-Flu, rituximab and a fludarabine-based regimen.

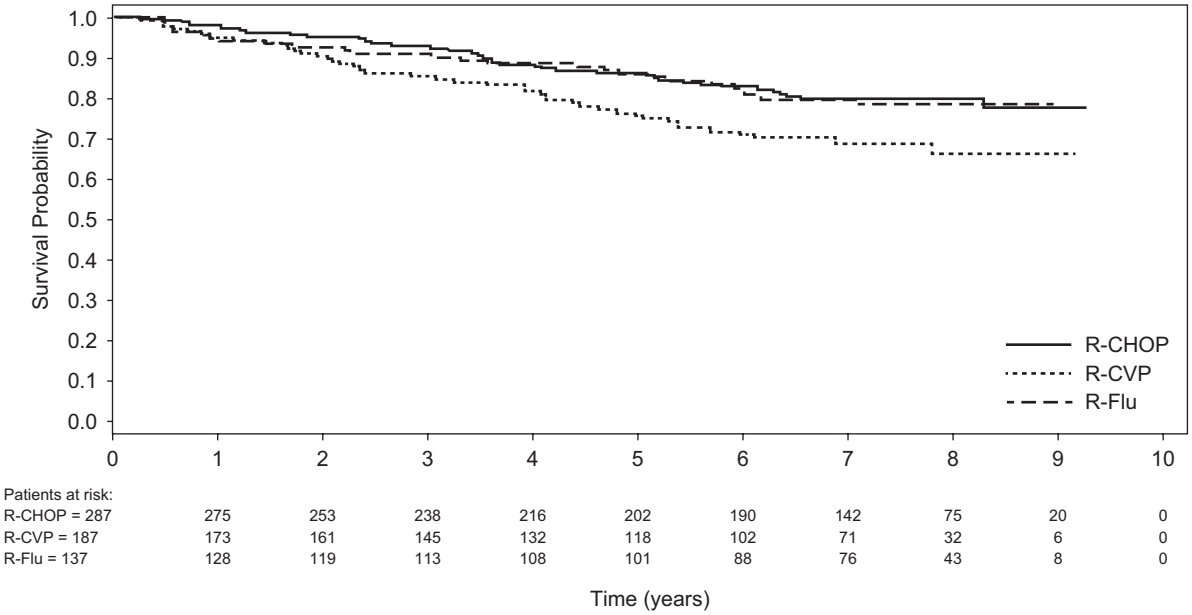


Figure 1. Kaplan–Meier estimates of overall survival for stage III/IV, grade 1/2 follicular lymphoma. R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone; R-CVP, rituximab plus cyclophosphamide, vincristine and prednisone; R-Flu, rituximab plus a fludarabine-based regimen.



their baseline characteristics was conducted to confirm the study results. These analyses identified and controlled for confounding factors, and present data for comparison with available randomized clinical trial results. Thus, these findings may support the causal inference drawn from the results of randomized trials.

We observed noticeable variation in the use of each frontline regimen. R-CHOP was administered two to one over R-CVP and almost five to one over R-Flu. During the period when these patients were diagnosed, treatment selection was primarily informed by parallel randomized clinical trials comparing chemotherapy alone with R plus chemotherapy [16–18]. A retrospective comparison of the frontline regimens used in the Primary Rituximab and Maintenance (PRIMA) phase III study also found that R-CHOP was the most commonly used regimen and that R-CHOP was associated with higher response rates and longer PFS compared with R-CVP [19]. Data from a randomized trial comparing the efficacy of R-CVP, R-CHOP and R-FM after a median follow-up of 34 months demonstrated that R-CVP was associated with an inferior 3-year time to treatment failure and PFS in comparison with R-FM and R-CHOP [20]. In concert with our findings, these results raise questions regarding the benefits of R-CVP, given the currently available treatment options.

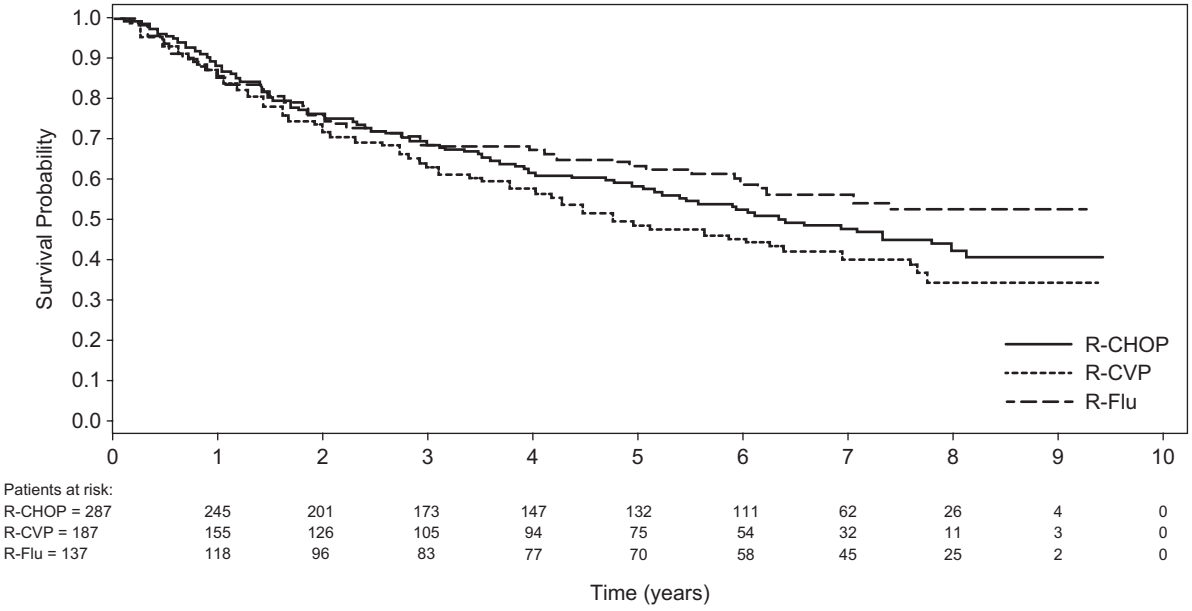


Figure 2. Kaplan–Meier estimates of progression-free survival for stage III/IV, grade 1/2 follicular lymphoma. R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone; R-CVP, rituximab plus cyclophosphamide, vincristine and prednisone; R-Flu, rituximab plus a fludarabine-based regimen.

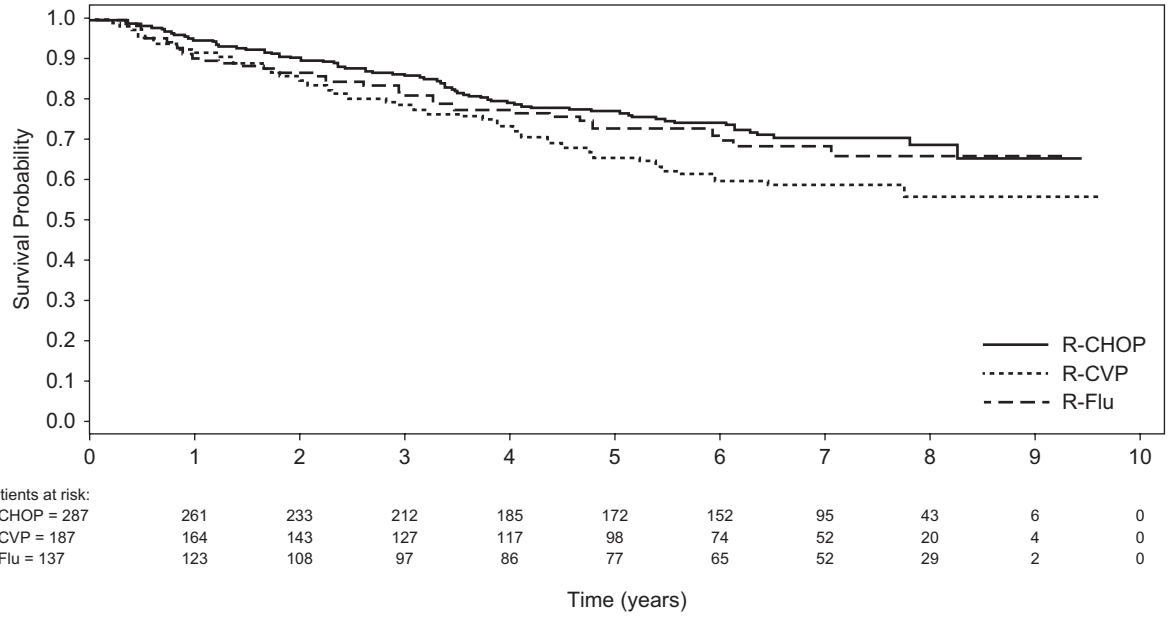


Figure 3. Kaplan–Meier estimates of transformation-free survival for stage III/IV, grade 1/2 follicular lymphoma. R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone; R-CVP, rituximab plus cyclophosphamide, vincristine and prednisone; R-Flu, rituximab plus a fludarabine-based regimen.



Additional treatment options exist that were not available as frontline therapy for the cohort of patients with FL diagnosed between 2004 and 2007. For instance, Rummel *et al.* reported a randomized phase III study showing that BR was superior to R-CHOP in terms of PFS (median PFS 69.5 months vs. 31.2 months, $p \leq 0.0001$) in advanced-stage, grade 1/2 FL, and appeared to be better tolerated [8]. Furthermore, preliminary results of an open-label, randomized study comparing BR with R-CVP and R-CHOP in first-line treatment of advanced indolent non-Hodgkin lymphoma [21] reported that BR harbors a distinct safety profile from that of R-CVP or R-CHOP. Thus, BR represents yet another viable option for physicians to consider when choosing frontline therapy in patients with advanced-stage, grade 1/2 FL. In addition, there is mounting evidence for targeting the immune response and/or tumor microenvironment in indolent non-Hodgkin lymphoma. Preliminary findings from phase II studies [22,23] indicate high response rates to R in combination with lenalidomide, a non-chemotherapy approach in untreated FL. On the basis of these findings, a phase III study (RELEVANCE; NCT01476787) is currently ongoing to examine the effectiveness of R and lenalidomide compared with chemoimmunotherapy for untreated FL with high tumor burden.

With prolonged follow-up in this study, we were able to examine late effects of frontline therapy. In this study, 89 patients developed a secondary malignancy. Of these, 10 patients developed MDS and four developed leukemia. The incidence of MDS or leukemia was similar among all three first-line regimens. Treatment-related MDS is of concern in indolent lymphoma, particularly since historically this disease is considered incurable with standard treatment and outcomes are improving. Up to 10% of patients with lymphoma treated with standard chemotherapy may develop treatment-related MDS [24]. McLaughlin *et al.* reported the occurrence of treatment-related MDS following fludarabine, mitoxantrone and dexamethasone (FND) with either concurrent or sequential R to be 3% at a median follow-up of 42 months [25]. An update of this study, with a median

Table IV. Comparison of PFS and OS for all patients*.

| | PFS | | OS | |
|---|---|---|---|---|
| | HR | 95% CI | HR | 95% CI |
| R-CVP | 1 | (Reference) | 1 | (Reference) |
| R-CHOP | 0.89 | 0.68–1.17 | 0.83 | 0.55–1.25 |
| R-Flu | 0.69† | 0.49–0.97 | 0.72 | 0.44–1.17 |

R-CVP, rituximab, cyclophosphamide, vincristine and prednisone; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; R-Flu, rituximab and a fludarabine-based regimen; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; OS, overall survival.
*All Cox proportional hazards models adjusted for sex, age (≤50, 51–60, 61–70 and >70 years), number of nodal sites, bone marrow involvement, lactate dehydrogenase, hemoglobin, geographic region, practice setting and a time-dependent variable for follow-on treatment (rituximab maintenance or observation).
†$p < 0.05$.

Table V. Propensity score adjusted estimates of PFS and OS for all patients by first-line treatment*.

| | Number of matched pairs | PFS | | OS | |
|---|---|---|---|---|---|
| | | HR | 95% CI | HR | 95% CI |
| R-CVP | | 1 | (Reference) | 1 | (Reference) |
| R-CHOP | 150 | 0.79 | (0.59–1.06) | 0.68 | (0.42–1.10) |
| R-Flu | 107 | 0.73 | (0.48–1.10) | 0.66 | (0.40–1.10) |

R-CVP, rituximab, cyclophosphamide, vincristine and prednisone; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; R-Flu, rituximab and a fludarabine-based regimen; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; OS, overall survival.
*Propensity scores were based on baseline factors: sex, age (≤50, 51–60, 61–70 and >70 years), number of nodal sites, lactate dehydrogenase, hemoglobin, bone marrow involvement, geographic region, practice setting, race, Eastern Cooperative Oncology Group performance status, stage, number of extranodal sites involved, histology and presence of B symptoms. The propensity score-matching model was estimated using the Cox regression model using matched pairs and the robust estimate of treatment variance, where patients were matched based on their propensity scores using the %GMATCH macro (source: mayoresearch.mayo.edu). The model was also adjusted for follow-on treatment (rituximab maintenance or observation).

Table VI. Secondary malignancy by first-line treatment.

| Malignancy, *n* (%*) | R-CHOP (*n* = 287) | R-CVP (*n* = 187) | R-Flu (*n* = 137) |
|---|---|---|---|
| Breast | 1 (0.3) | 2 (1.1) | 1 (0.7) |
| Lung | 7 (2.4) | 3 (1.6) | 2 (1.5) |
| MDS | 3 (1.0) | 3 (1.6) | 4 (2.9) |
| Leukemia | 2 (0.7) | 1 (0.5) | 1 (0.7) |
| Colon | 1 (0.3) | 2 (1.1) | 0 |
| Brain | 0 | 1 (0.5) | 1 (0.7) |
| Skin | 13 (4.5) | 8 (4.3) | 5 (3.6) |
| Prostate | 5 (1.7) | 4 (2.1) | 2 (1.5) |
| Kidney | 2 (0.7) | 1 (0.5) | 1 (0.7) |
| Pancreas | 1 (0.3) | 1 (0.5) | 0 |
| Other | 10 (3.5) | 8 (4.3) | 9 (6.6) |
| Total number of patients* | 38 (13.2) | 27 (14.4) | 24 (17.5) |

MDS, myelodysplastic syndrome; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; R-CVP, rituximab, cyclophosphamide, vincristine and prednisone; R-Flu, rituximab and a fludarabine-based regimen.
*Patients may have experienced more than one secondary malignancy.



follow-up of over 12 years, reported an occurrence of MDS/acute myeloid leukemia of 5% [26]. In this study, we observed an occurrence of MDS or leukemia to be as low as 1.7% in the R-CHOP group and as high as 3.6% in the R-Flu group.

We observed 8-year estimates for TFS of 55% in the R-CVP group and 69% in the R-CHOP group. Our analysis was restricted to patients of low-grade, advanced-stage FL, but it provides meaningful information regarding the rate of transformation in the chemoimmunotherapy era. Based on population-based series in the pre-R era, actual risk of transformation was reported to be continuous at 3% per year and was associated with a median survival of less than 2 years [27]. In the chemoimmunotherapy era, the rate of transformation may be improving, with reports of an estimated rate of 2% per year, with median OS post-transformation of 50 months [28]. Additional analyses using the NLCS dataset are ongoing, examining outcomes following transformation in the R era, and are eagerly awaited [29].

We observed that patients in the R-CVP group were older and more commonly female and more frequently harbored high-risk FLIPI scores. Interestingly, the majority of these patients received R maintenance. It is possible that maintenance use impacted outcomes for patients who received R-CVP even after model adjustments. Among the individual components of the FLIPI score, age was the only component that differed significantly across groups, suggesting that the difference in FLIPI for the R-CVP group most likely reflected the difference in age alone. Our finding that R-CVP was more commonly selected than R-CHOP in patients over the age of 70 years was perhaps based upon concerns regarding anthracycline toxicity in this older population, and a lack of perceived differential benefit for anthracycline-based therapy in FL [30]. Gender bias resulting in less anthracycline use among female patients also may be associated with concerns regarding anthracycline toxicity, such as alopecia. Chemotherapy-induced alopecia can be psychologically devastating [31–36] and may explain the observed gender differences. Extreme anxiety regarding this side effect of treatment has reportedly influenced the decision to reject chemotherapy in some patients [37]. It is less clear why regional variations in treatment selection were observed. These practice patterns may represent systematic variations in treatment selection that are not data driven and may or may not improve outcomes.

The goal of comparative effectiveness research is to understand outcomes of treatments as they are utilized by real-world practitioners who face everyday treatment decisions for patients whose attributes do not exactly correspond to clinical trial eligibility criteria. This is the largest prospective observational study reporting on the real-life effectiveness of frontline chemoimmunotherapy with over 7 years of median follow-up. As these results show, all commonly used regimens have high ORR and robust 5-year PFS and OS when combined with extended R dosing strategies and the options available for salvage therapy. For grade 1/2, advanced-stage FL, R-CHOP and R-CVP were similar in terms of PFS even in patients with high-risk FLIPI scores. R-Flu was associated with superior PFS compared with R-CVP, but was more commonly discontinued because of toxicity, and was less commonly used, perhaps owing to concerns about tolerability. With longer follow-up, the 5- and 8-year estimates suggest inferior outcomes associated with R-CVP.

These analyses do not account for how much of the selected frontline therapy was delivered, and future studies are needed to define the most effective sequence of therapy, given the heterogeneity in treatment at relapse for this patient population. With the long-term toxicity profile of BR not well appreciated at this time [9], and concerns about toxicity associated with R-Flu, the optimal frontline therapy for advanced-stage FL remains undefined. We observed favorable outcomes with frontline chemoimmunotherapy in this large observational study. With clinical trials examining non-chemotherapy strategies for low-grade lymphoma, this study highlights the importance of prolonged follow-up to examine the effectiveness of frontline therapy for low-grade lymphoma and the continued value in using these revise hyphenation to read “chemo - immunotherapy” regimens as comparators.

***Potential conflict of interest:*** Disclosure forms provided by the authors are available with the full text of this article at www.informahealthcare.com/lal.

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