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ORIGINAL ARTICLE

Impact of immunochemotherapy with R-bendamustine or R-CHOP for treatment naïve advanced-stage follicular lymphoma: A subset analysis of the FOLL12 trial by Fondazione Italiana Linfomi

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Abstract

We conducted a post hoc analysis of the FOLL12 trial to determine the impact of different initial immunochemotherapy (ICT) regimens on patient outcomes. Patients were selected from the FOLL12 trial, which included adults with stage II–IV follicular lymphoma (FL) grade 1–3a and high tumor burden. Patients were randomized 1:1 to receive either standard ICT followed by rituximab maintenance (RM) or the same ICT followed by a response-adapted approach. ICT consisted of rituximab-bendamustine (RB) or rituximab, cyclophosphamide, doxorubicin, and prednisone (R-CHOP), per physician's decision. A total of 786 patients were included in this analysis, 341 of whom received RB and 445 R-CHOP. RB was more frequently prescribed to older subjects, females, patients without bulky disease, and those with grade 1–2 FL. After a median of 56 months of follow-up, R-CHOP and RB had similar progression-free survival (PFS) (Hazard Ratio for RB 1.11, 95% CI 0.87–1.42, $p = 0.392$). Standard RM was associated with improved PFS compared to response-adapted management both after R-CHOP and RB. Grade 3–4 hematologic adverse events were more frequent with R-CHOP during induction treatment and more frequent with RB during RM. Grade 3–4 infections were more frequent with RB. RB was also associated with a higher incidence of transformed FL. R-CHOP and RB

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showed similar activity and efficacy, but with different safety profiles and long-term events, suggesting that the treating physician should carefully select the most appropriate chemotherapy regimen for each patient based on patient's individual characteristics, choices, and risk profile.

KEYWORDS
follicular lymphoma, immunochemotherapy, survival

1 | INTRODUCTION

Follicular lymphoma (FL) is the most frequent among indolent lymphomas and accounts for 20% of all Non Hodgkin Lymphoma (NHL) cases. Although the disease is characterized by a relapsing and remitting clinical course, it is associated with excellent outcomes, with a median survival measured in decades. The administration of immunochemotherapy (ICT) followed by rituximab maintenance (RM) is the recommended approach for front-line therapy of patients with high tumor burden (HTB).[1] Among the ICT regimens available, rituximab-bendamustine (RB) and rituximab cyclophosphamide doxorubicine, vincristine and prednisone (R-CHOP) are the preferred options. The StiL and the BRIGHT randomized trials[2–4] compared these two regimens, with results in terms of progression-free survival (PFS) being discordant. However, both trials reported no differences between the two regimens in terms of overall survival, and both showed less grade 3–4 neutropenia, alopecia, peripheral neuropathy, and/or mucositis after RB compared to R-CHOP. However, in the long-term update of the BRIGHT study, a slight increase in the rates of secondary malignancies associated with RB was reported.[2–4]

Regarding RM, its use after R-CHOP is strongly supported by the results of the PRIMA randomized trial[5,6]; conversely, no prospective data are available to confirm the efficacy of RM in patients initially treated with RB.

The FOLL12 trial was conducted to demonstrate that a response-adapted post-induction management of patients with high tumor burden (HTB) FL could be as effective as standard RM in terms of PFS. The trial showed the better efficacy of standard RM compared to the experimental approach, thus providing an indirect confirmation of the efficacy of RM after ICT.[7] This post hoc study compared RB and R-CHOP in terms of the outcomes of patients enrolled in the FOLL12 study, which was initially designed with R-CHOP as ICT but which was amended to allow the use of RB as a second ICT option after the first 227 patients had been enrolled.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

FOLL12 is a multicenter, randomized, phase III trial that compared standard RM with response-adapted post-induction management in treatment-naïve patients with grade 1–3a, stage II–IV, high tumor burden (HTB) FL. More details on patient selection criteria are provided in the appendix.

The study, conducted in compliance with the Declaration of Helsinki and approved by the appropriate Ethics Committee, required that each patient give written informed consent before registration and random assignment (ClinicalTrials.gov identifier: NCT02063685).

2.2 | Procedures

In the FOLL12 trial, eligible patients were centrally and randomly assigned to one of the two study arms before treatment start and were stratified by FLIPI2 score (1–2 vs. 3–5).[8] When the study started, all patients were scheduled to receive CHOP in combination with rituximab (R-CHOP). In April 2014, the study protocol was amended to allow the use of bendamustine as an alternative to CHOP, leaving the choice of the chemotherapy regimen to the treating physician on a patient-by-patient basis. The decision to amend the protocol was taken after the Italian Ministry of Health and the Italian Medicines Agency (AIFA) approved the use of bendamustine as first-line therapy for FL. Regardless of the chemotherapy prescribed, all patients received induction ICT with six cycles of either R-CHOP or RB, both followed by two additional doses of rituximab. After the study was amended, randomization was modified by adding the type of chemotherapy as a stratification factor. After ICT, patients in the standard treatment arm received bimonthly rituximab for up to 2 years, while patients in the experimental arm were managed according to centrally reviewed metabolic and molecular response. Patients achieving complete metabolic (CMR) and molecular response were managed with observation only; those in CMR with molecular persistence received one weekly rituximab dose for 4 weeks. Patients not achieving CMR were treated with radioimmunotherapy with ibritumomab tiuxetan, followed by standard RM.

2.3 | Outcomes

This analysis was conducted as a post hoc long-term observational study of patients enrolled in the FOLL12 trial.

The study endpoints of this long-term analysis were response rate (RR), progression-free survival (PFS), overall survival (OS), frequency of adverse events (AEs), cumulative incidence of secondary malignancies (SM), and transformed FL (tFL).

RR was assessed using the 2007 revised criteria for NHL and the Lugano 2014 criteria. PFS was defined as the time from date of study entry to the date of last contact, disease progression, relapse, or death resulting from any cause in patients with FL. OS was calculated as the time from study entry until the date of last follow-up or death for any cause. AEs were registered in accordance with the standard Common Terminology Criteria for Adverse Events (CTCAE).

A complete description of the statistical methods used is reported in the Supplemental Material. The data were updated in September 2022.

3 | RESULTS

3.1 | Patient characteristics and treatment

A total of 786 eligible patients were enrolled and randomized 1:1 to either the standard or the experimental arm: 445 patients received R-CHOP, including 227 treated before the protocol amendment, and 341 received RB (Supplemental Figure 1).

The main characteristics of eligible patients are reported in Table 1. RB was more frequently prescribed in older and in female patients (odds ratio [OR] 1.6, $p = 0.001$), whereas R-CHOP was the preferred option in patients with bulky disease (>6 cm) and with grade 3a histology (OR 0.65, $p = 0.013$). No differences in the characteristics of the patients treated with R-CHOP before and after the protocol amendment were observed.

3.2 | Response to induction treatment

All planned cycles of induction ICT were administered to 90% (712) of patients (93% in R-CHOP and 88% in R-B group): 58% (299) with RB and 41% (413) with R-CHOP. The radiological complete remission (CR) rate to ICT was similar between the two treatment groups (R-CHOP vs. RB, 77% vs. 78%; $p = 1.06$); however, the overall RR was higher for patients in the R-CHOP group than those in the RB group (93% vs. 89%; $p = 0.021$). Only considering patients who achieved at least PR, treatment with R-CHOP achieved similar rates of metabolic (90% vs. 92%, respectively) and molecular response (84% vs. 87%, respectively) as with RB (Supplemental Table 1).

3.3 | Survival analysis

After a median follow-up of 56 months (range 1–97), 271 PFS events were recorded. The 5-year PFS rate was 64% (95% CI 60–67). In the non-randomized comparison between RB and R-CHOP, no difference in terms of PFS was observed between the two regimens (hazard ratio [HR] for RB 1.11, 95% CI 0.87 to 1.42, $p = 0.392$) (Figure 1). No statistically significant difference in terms of PFS was observed when the comparison was adjusted for the main confounding factors (sex, age, hemoglobin [Hb], bone marrow [BM] involvement, bulky disease, beta-2 microglobulin [B2M], number nodal sites [NS], lactate dehydrogenase [LDH], B symptoms, absolute lymphocyte counts, longest diameter of largest lymphnode [LodLIN], and randomized arm). We also conducted a stabilized inverse probability weighting (IPW) analysis accounting for sex, age, Hb, BM, B2M, LodLIN, NS, LDH, B symptoms, and randomized arm), which confirmed a lack of difference in PFS between the two groups (HR 1.20, 95% CI 0.93–1.54, $p = 0.152$). The interaction between patients' characteristics and induction ICT is reported in Supplemental Figure 2.

Examining PFS by randomization arm, patients assigned to standard treatment achieved better PFS compared to those randomized to the response-adapted management, regardless of

TABLE 1 Patient characteristics ($N = 786$).

Factor	R-CHOP ($N = 445$) *n* (%)	RB ($N = 341$) *n* (%)	Total ($N = 786$) *n* (%)	*p*-value	OR (95% CI)	Missing
Age >60	189 (42)	202 (59)	391 (50)	<0.001	1.97 (1.48–2.62)	-
Female sex	212 (48)	202 (59)	414 (53)	0.002	1.60 (1.20–2.12)	-
Grade 3a	123 (28)	68 (20)	191 (24)	0.015	0.65 (0.46–0.91)	-
B symptoms	116 (26)	41 (12)	157 (20)	<0.001	0.39 (0.27–0.58)	6
Bone marrow+	256 (58)	181 (53)	437 (56)	0.219	0.84 (0.63–1.11)	-
Stage III-IV	402 (91)	295 (87)	697 (89)	0.134	0.70 (0.45–1.10)	3
Hb <12 g/dL	69 (16)	58 (17)	127 (16)	0.625	1.12 (0.76–1.64)	-
LodLIN >6 cm	266 (60)	169 (50)	435 (55)	0.005	0.66 (0.50–0.88)	-
B2M > ULN	240 (54)	187 (55)	427 (54)	0.829	1.04 (0.78–1.38)	-
Nodal sites >4	190 (43)	129 (39)	319 (41)	0.239	0.83 (0.62–1.12)	10
LDH > ULN	106 (24)	67 (20)	173 (23)	0.256	0.81 (0.57–1.14)	20
FLIPI-2 3/5	172 (39)	144 (42)	316 (40)	0.340	1.16 (0.87–1.55)	-
Experim. arm	232 (52)	161 (47)	393 (50)	0.195	0.82 (0.62–1.09)	-

whether initially treated with R-CHOP or with RB (HR R-CHOP 1.60, 95% CI 1.17–2.18; HR RB 1.81, 95% CI 1.24–2.64) (Figure 2).

3.4 | Safety

We analyzed grades 3 and 4 AEs in the induction and post-induction phases separately. During induction therapy, the most common AEs in both treatment arms were cytopenia, infections, and cutaneous events. Grade 3–4 neutropenia was more frequently observed in R-CHOP (43.7%) than in RB (32.6%) (relative risk RR 0.75; $p = 0.002$), as was febrile neutropenia (2.7% vs. 0.6%, respectively; RR 0.22; $p = 0.030$). Among extra-hematologic AEs, higher frequencies of infections and of cutaneous events were observed in RB-treated patients (3.2% vs. 1.4%, $p = 0.086$% and 2.1% vs. 0.2%, $p = 0.024$). (Table 2).

In the post-induction phase, we excluded 23 patients treated with radioimmunotherapy from the safety analysis and separated the remaining patients into two further groups according to randomization arm. In the group of patients randomized to standard RM, those treated with RB were more frequently affected by grade 3–4 neutropenia than those in R-CHOP (17.6 vs. 8.8%; $p = 0.015$). Similar rates of grade 3–4 hematologic events were seen in the experimental arm for both the R-CHOP and the RB groups. Extra-hematologic AEs during the post-induction phase were low in both the experimental and the standard arms for R-CHOP and RB (Table 2).

During follow-up, 58 s malignancies (SM) were reported after the end of induction therapy (Supplemental Table 2), including 25 hematologic malignancies and 33 solid cancers. The cumulative incidence function (CIF) of SM (excluding nonmelanoma skin cancers) at 5 years was 9.9% (95% CI 7.4–12.8). The CIF of SM was higher in patients treated with RB than in those treated with R-CHOP (5-yr CIF% 11.6% vs. 8.2, respectively; sHR 1.79, 95% CI 1.08–3.00, $p = 0.025$) (Supplemental Figure 3). Correcting data for demographic features (age and sex), the risk of developing an SM in patients treated with RB decreased, with HR 1.61 (95% CI. 0.95–2.73, $p = 0.076$) (Supplemental Table 3).

Thirty-three transformed FL (tFL) since the start of treatment were identified, with a 5-year cumulative incidence of tFL of 4.5% (95% CI 3.1%–6.4%). The risk of developing tFL was higher for patients treated with RB than for those treated with R-CHOP (HR 2.43, 95% CI 1.18–5.0, $p = 0.015$) (Figure 3).

Overall, 71 deaths were reported: 39 in the R-CHOP group and 32 in the RB group. The main causes of death were lymphoma progression (30), followed by second cancer (7) and other causes (34). Causes of death were similar in patients treated with RB and with R-CHOP (Table 3). The 5-year OS rate was 93% (95% CI 90–95) in the R-CHOP group and 88% (95% CI 83–92) in the RB group (HR 1.81, 95% CI 1.10–2.97; $p = 0.020$) (Supplemental Figure 4). When the interaction with age and with sex was analyzed, a difference for OS was only confirmed for patients aged 50–59 years (HR 3.06, 95% CI 1.05–8.88; $p = 0.04$) (Supplemental Table 4).

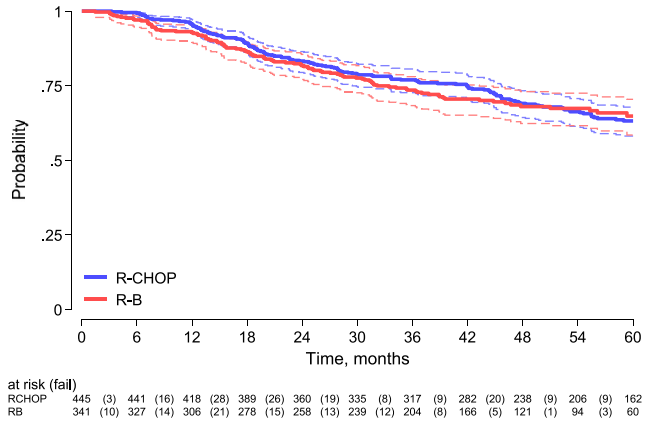

FIGURE 1 Progression-free survival by induction immunochemotherapy (non-randomized comparison, $N = 786$).

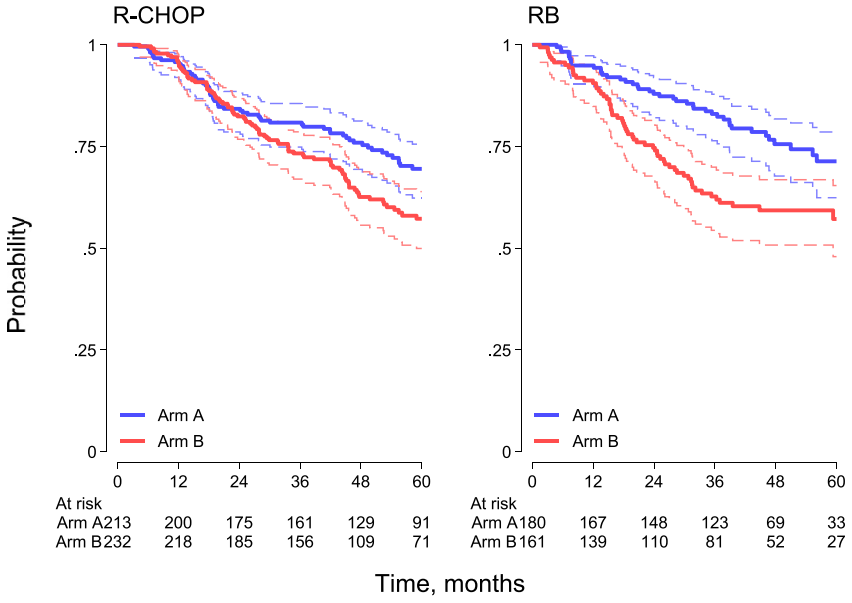

FIGURE 2 Progression-free survival for standard **(Arm A)** and response-adapted management **(Arm B)** according to R-CHOP and RB initial treatment.

TABLE 2 Hematologic and extra-hematologic adverse events CTCAE >2 during induction and post-induction therapy.

Adverse events	Induction		Post-induction			
	n = 437	*n* = 324	Standard arm		Experimental arm	
Grade 3–5	R-CHOP (%)	RB (%)	R-CHOP (%)	RB (%)	R-CHOP (%)	RB (%)
Anemia	2.0	0.6	0	1.3	1.4	0
Leukopenia	7.0	5.0	0	1.3	1.0	2.2
Neutropenia	43.7	32.6	8.8	17.6	6.2	9.7
Thrombocytopenia	1.1	1.2	0	0.7	3.8	3.0
Febrile neutropenia	2.7	0.6	0	0.7	0	0
Cardiac disorders	1.6	0.6	1.6	0	2.4	0
Endocrine disorders	0.2	0	0	0	0	0.7
Gastrointestinal	2.9	1.8	0.5	0	1.0	0.7
General disorders	1.4	0.6	0	0.7	0	0
Infections	1.4	3.2	2.6	0	1.9	0.7
Investigations	0	0.9	0	0	0	0.7
Metabolism	0.2	0.6	0	0	0.5	0
Musculoskeletal	0.2	0.6	0	0.7	0	0
Neoplasm	0	0.3	0	1.7	2.9	1.5
Nervous system	1.4	0.6	0.5	0	0.5	2.2
Psychiatric	0.2	0	0	0	0.5	0
Renal disorders	0.7	0.6	0	0.7	0	0.7
Reproductive	0	0	0	0	0.5	0
Respiratory	1.1	0.6	0	0	1.0	0
Skin/subcutaneous	0.2	2.1	0	0	0	0.7
Vascular disorders	0.2	0.3	0	0	0	0
Others	1.8	3.8	0	0.7	1.0	0.7

Note: Induction: 444 RCHOP, 340 RB (tot 784/786, 99.7%). Post-induction: patients in CR/PR after completing the induction cycles (6–8 cycles). Standard arm: 193 RCHOP, 153 RB (tot 346). Experimental arm: 209 RCHOP, 134 RB (tot 343). Overall 689/712 (96.8%). Others: congenital disorders, ear and labyrinth, hepatobiliary, immune system, injury/complications and other rare adverse events.

We were able to calculate progression of disease within 24 months from diagnosis (POD24) in 741 patients; 123 cases were considered as POD24 (17%) and were associated with a shorter OS (Supplemental Figure 5A). POD24 was reported for 69/429 (16%) and for 54/312 (17%) of cases treated with R-CHOP or RB, respectively (OR 1.09, 95% CI 0.74–1.61, $p = 0.659$) (Supplemental Figure 5B). No difference in the POD24 rates was observed between the two regimens when the analysis was adjusted for FLIPI2, randomized therapy, and sex (OR 1.15, 95% CI 0.77–1.72, $p = 0.490$).

4 | DISCUSSION

The non-randomized comparison between R-CHOP and RB conducted on patients enrolled in the randomized FOLL12 trial demonstrated similar activity and efficacy of the two regimens for the initial treatment of high tumor burden FL patients. In both the RB and the R-CHOP groups, standard maintenance therapy led to significantly improved PFS compared to the response-adapted post-induction therapy used in the FOLL12 trial, thus providing an indirect demonstration of the efficacy of RM therapy after RB as well. Differences in the early and late safety profiles of RB and R-CHOP were observed.

The data reported in this study contribute to better defining the risk-benefit profile of both R-CHOP and RB, although which is the best choice for the first-line treatment of FL remains controversial. When examining the results of the two published randomized trials that included a comparison between R-CHOP and RB, our data suggest similar anti-lymphoma efficacy of the two regimens, in line with the results of the BRIGHT study. However, unlike the BRIGHT trial, our study was limited to only FL, included more patients, and did not include rituximab, cyclophosphamide, vincristine and prednisone (R-CVP) in the comparison.[2,3] Also, both the BRIGHT and the STIL trials were randomized, while our analysis was not.[4] The lack of

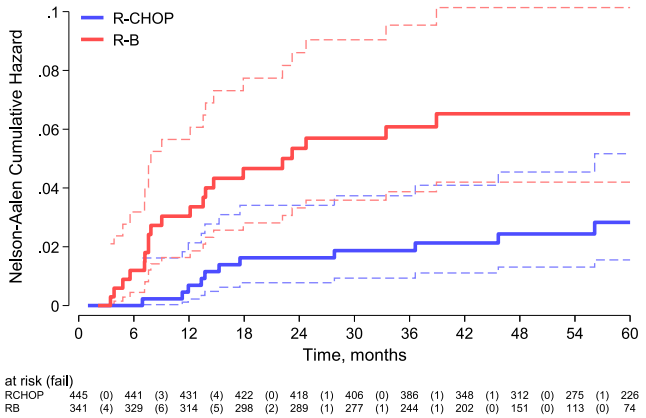

FIGURE 3 Cumulative incidence of transformed follicular lymphoma after end of induction ($N = 712$) by R-CHOP and RB initial treatment.

TABLE 3 Causes of death overall and by induction treatment.

Cause	R-CHOP, *n*	RB, *n*	Total, *n*
Progression	18 (46%)	12 (38%)	30 (42%)
Second cancer	3	4	7
Sepsis (3 COVID-19)	5	3	8
Neurological disorders	1	2	3
Cachexia	1	1	2
Heart failure	3	-	3
Toxicity during treatment	-	1	1
Stroke	-	1	1
Autoimmune encephalitis	1	-	1
Unknown	7	8	15
Total	**39**	**32**	**71**

randomization and the fact that RB could be used only in a later phase of study represent the major limitations of our study, as the results may have been influenced by imbalances in the baseline clinical characteristics of the population. Indeed, patients treated with bendamustine in the FOLL12 study were older than those in the CHOP group and also had a better prognostic profile (less high-risk FLIPI, fewer males, fewer bulky lesions). We managed these acknowledged limitations by adopting statistical methods, such as propensity score-matched analyses for PFS comparisons, to simulate randomization. Notably, differences in patient characteristics between RB and R-CHOP were very similar to those observed in the post hoc analysis conducted for the GALLIUM trial, which compared rituximab with obinutuzumab-based induction ICT followed by maintenance in newly diagnosed FL patients. The GALLIUM trial involved three different chemotherapy options–bendamustine, CHOP, or CVP–leaving the choice to each center participating in the trial.[9]

Patients treated with R-CHOP in the FOLL12 study were more frequently diagnosed as FL grade 3a than those in the RB group. Grade 3a histology has been suggested as a risk factor for worse outcome and for tFL in patients treated in the pre-rituximab era,[10] but this finding has never been confirmed in the setting of immunochemotherapy.[11] Nevertheless, many physicians still prefer to use anthracyclines to mitigate the risk of transformation in patients with grade 3a FL. Looking at our results, we are not able to reach any conclusion concerning which had better efficacy in the group of FL3a, R-CHOP or RB; Overall response rates (ORR), 5-year PFS, and OS for RB versus R-CHOP were superimposable for grade 3a FL (93% vs. 89%, $p = 0.021$; 65% vs. 66%, $p = 0.685$; 94% vs. 91% $p = 0.210$, respectively), and the risk of tFL was very low in both treatment groups (2% vs. 2.7%; R-CHOP vs. RB).

Overall, the cumulative risk of tFL was very low for the whole study population, in line with recent observations,[12,13] suggesting that the modern approach to FL staging, combined with the excellent disease control achieved by effective ICT, may have an important role in reducing the risk of tFL. Despite the context of a very low risk of tFL, we were still able to show higher rates of tFL associated with RB than with R-CHOP. This finding suggests a less protective role of RB for tFL and is consistent with high tFL rates observed after RB by another group.[14]

The FOLL12 trial provided an indirect demonstration of the efficacy of RM for patients who responded to induction ICT. This finding was confirmed for patients initially treated with both CHOP and bendamustine. RM after bendamustine was suggested as effective in a retrospective analysis of 640 patients treated at the MD Anderson Cancer Center. In that study, duration of response (DOR) was improved by RM mainly for patients achieving a PR after RB induction, with only a trend observed for those in CR.[15] A similar observation was reported in the long-term analysis of the BRIGHT study, which allowed RM at the physician's discretion for patients responding to ICT. In the BRIGHT study, RM was prescribed to 43% and 45% of patients treated with RB or R-CHOP/R-CVP, respectively, and was associated with improved PFS in both treatment groups.[2] The efficacy of RM in patients initially treated with bendamustine is a relevant finding from our study that confirms improved PFS with RM in all patients who achieve a complete metabolic response after ICT.

Regarding toxicity, our results are in line with findings from other trials on the safety profile of induction therapy. Hematologic toxicity was more frequent in R-CHOP than in RB (grade 3–4 neutropenia 44% vs. 33%, respectively), but R-CHOP was associated with less frequent extra-hematologic AEs, including infections and cutaneous events (1.4% vs. 3.2%, respectively, $p = 0.086$, and 0.2 vs. 2.1%, respectively, $p = 0.024$). The increased risk of infections in the group of patients treated with bendamustine was also observed in the GALLIUM trial, which shares our limitation of a non-randomized comparison, but which provided a biologic rationale for these findings, showing more profound impairment of the dynamics of the CD8 + T cell in patients treated with bendamustine compared with those treated with CHOP.[9,16]

In addition to the description of the safety profile of the induction phase, we were also able to observe the toxicity profile of RB and R-CHOP in the post-induction phase and during follow-up. In this

analysis, RB was associated with more hematologic events, and in particular with higher rates of severe neutropenia, compared with R-CHOP, but this finding was only observed for the standard maintenance arm (17.6 vs. 8.8%, respectively; $p = 0.015$).

Finally, the incidence of second malignancies (excluding non-melanoma skin cancers) was similar in patients treated with RB and those with R-CHOP when the analysis was adjusted for age and sex.

The increase in late events and the slight increase in tFL observed for patients treated with RB could explain the statistically significant difference in the risk of death for patients treated with this regimen, which was annulled when the analysis was adjusted for age and sex for all patients, with the exception of those aged 50–59 years. This finding might have been biased by the non-randomized allocation of ICT and would be confirmed by a longer follow-up.

5 | CONCLUSION

In conclusion, this post hoc analysis of the FOLL12 trial showed that R-CHOP and RB are associated with similarly high efficacy in the initial treatment of HTB FL and that RM can further improve PFS when used after induction treatment, even when optimal response to ICT has been achieved. Considering the differences in safety profile between RB and R-CHOP, our data can be used to discuss with the patient the risk-benefit ratio of any initial treatment choice. This aspect is particularly important when other competing risks to the patient's safety are present.

AUTHOR CONTRIBUTIONS

Massimo Federico, Stefano Luminari and Maria E. Nizzoli designed the study. Luigi Marcheselli performed the statistical analyses. All authors provided study material, performed interpretation of data, and approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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