Rituximab and lenalidomide for the treatment of relapsed or refractory indolent non-Hodgkin lymphoma: real-life experience

Giulio Cassanello,[1,2] Esther Drill,[3] Alfredo Rivas-Delgado,[1] Michelle Okwali,[1] Irem Isgor,[4] Philip C. Caron,[1,5] Zachary Epstein-Peterson,[1,5] Paola Ghione,[1,5] Paul A. Hamlin,[1,5] Jennifer K. Lue,[1,5] Steven M. Horwitz,[1,5] Andrew M. Intlekofer,[1,5] William Johnson,[1,5] Anita Kumar,[1,5] Alison J. Moskowitz,[1,5] Ariela Noy,[1,5] Colette N. Owens,[1,2] M. Lia Palomba,[1,5] Pallawi Torka,[1,5] Pallavi Galera,[4,5] Andrew D. Zelenetz,[1,5] Gilles A. Salles[1,5] and Lorenzo Falchi[1,5]

[1]Department of Medicine, Lymphoma Service, Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]Department of Oncology and Hemato-Oncology, University of Milan, Milan, Italy; [3]Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY, USA; [4]Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, NY, USA and [5]Department of Medicine, Weil Cornell Medical College, New York, NY, USA

Correspondence: L. Falchi
falchil@mskcc.org

Received: April 15, 2024.
Accepted: August 27, 2024.
Early view: September 5, 2024.

https://doi.org/10.3324/haematol.2024.285600

Abstract

The combination of rituximab and lenalidomide (R-len) stands as an established treatment for relapsed/refractory (R/R) indolent non-Hodgkin lymphoma (iNHL). However, the reproducibility of clinical trial results in routine clinical practice is unknown. To address this gap in knowledge, we reviewed our experience with patients diagnosed with R/R follicular lymphoma (FL) or marginal zone lymphoma (MZL) treated with this combination.

Eighty-four patients underwent treatment with R-len, 69 (82%) affected by FL and 15 (18%) by MZL. The median age at the time of treatment initiation was 65 years (range, 39-94), 38 patients (45%) had a pretreatment FLIPI score of 3-5, 19 (23%) had a bulky disease, 29 (37%) had a lymphoma refractory to the last treatment line, while in 20 (24%) cases the disease was refractory to rituximab. The best overall response rate was 82%, and 52% achieved a complete response (CR). The best CR rates for FL and MZL patients were 55% and 40%, respectively. With a median follow-up of 22 months, the median progression-free survival was 22 months (95% confidence interval [CI]: 19-36) and the 2-year overall survival was 83% (95% CI: 74-93). The median duration of CR was 46 months (95% CI: 22-not reached). Factors associated with shorter progression-free survival in multivariate analysis were bulky disease and rituximab refractoriness. The most common adverse events included hematologic toxicity, fatigue and gastrointestinal disorders, such as diarrhea and constipation. Neutropenia and thrombocytopenia were the most common severe toxicities (grade ≥3 in 25% and 4%, respectively). No new safety signals were reported. Real-life results of R-len in patients with R/R iNHL appear consistent with those reported in prospective studies, and further support its use as comparator arm in controlled clinical trials.

Introduction

Indolent non-Hodgkin lymphomas (iNHL) encompass a heterogeneous group of B-cell neoplasms characterized by smoldering clinical course, frequent response to therapy, and a tendency to relapse over time.[1] Follicular lymphoma (FL) and marginal zone lymphoma (MZL) represent 22% and 7% of adult NHL,[2] respectively and, while biologically distinct, are often treated following similar paradigms.[3,4] Treatment options for patients with relapsed or refractory (R/R) FL or MZL are varied and a standard of care is not established beyond the first line of treatment.[5,6] The combination of lenalidomide and an anti-CD20 monoclonal antibody has emerged as an accepted treatment, based on preclinical models suggesting synergism between these agents[7-9] and subsequent clinical studies showing compelling activity and a manageable safety profile.[10,11]

In the randomized phase III AUGMENT trial, 147 patients with R/R FL and 31 patients with R/R MZL were assigned to receive lenalidomide and rituximab (R-Len) and had a significant improvement in progression-free survival (PFS) compared to those treated with rituximab alone,[10] with a sustained benefit observed over an extended period.[12,13] Based on the results of AUGMENT, R-Len has been approved

by the US Food and Drug Administration for the treatment of R/R FL.[14] Similarly, in a phase II trial in patients with R/R FL and R/R MZL the lenalidomide and obinutuzumab combination produced encouraging efficacy, with a 2-year PFS of 65% and a manageable safety profile.[11]

These results underscore the therapeutic benefits of lenalidomide plus anti-CD20 antibodies and led to the acceptance of this combination as standard of care in modern comparative clinical trials in patients with R/R iNHL.[15–17] However, the reproducibility of trial data in the real world is currently unknown.[12-14] Therefore, we set out to describe the safety and efficacy of R-len in a real-life context, and analyzed the determinants of response and outcomes.

Methods

Study population and treatment

We searched our electronic database to collect disease, treatment, and outcome information. We included consecutive, fully annotated adult patients with R/R FL or MZL who underwent treatment with R-len at Memorial Sloan Kettering Cancer Center. Rituximab was administered at 375 mg/m^2 weekly for 4 weeks, then every 28 days during cycles 2 to 5. The planned starting dose of lenalidomide was 20 mg orally daily for 21 out of 28 days for 12 28-day cycles. Additional cycles, dose modifications or delays were at the physician's discretion. This retrospective study received approval from our center's Institutional Review Board.

Efficacy and safety assessments

The primary objectives of this analysis were to assess the rates of best response and PFS. Secondary endpoints included safety of the combination, the end of treatment (EOT) response rate, duration of complete response (DoCR), event-free survival (EFS), and overall survival (OS), as well as an analysis of determinants of efficacy.

Disease response was assessed according to the 2014 Lugano criteria[18] for patients with nodal disease, while the 2020 European Society for Medical Oncology (ESMO) guidelines were adopted for those with splenic MZL (SMZL) and extranodal MZL (EMZL).[4] One patient was not evaluable for best response and was classified as not achieving an objective response according to "intent to treat" principles. PFS was defined as the time from treatment initiation to disease progression or death, whichever occurred first. Patients who underwent stem cell transplantation consolidation, or commenced another therapy due to stable disease (SD) after R-len, were censored at that time. EFS was defined as the time from treatment initiation to disease progression, death, or new treatment start, whichever occurred first. DoCR denoted the period from the achievement of CR to disease progression or death; OS was defined as the time from treatment initiation to death from any cause.

Adverse events (AE) were adjudicated and graded retrospectively through manual chart review in accordance with the Common Terminology Criteria for Adverse Events (CTCAE) version 5.[19]

Next-generation sequencing analysis

In a subset of FL patients, genomic profiling was performed on pretreatment tumor samples using a clinically validated next-generation sequencing (NGS) panel interrogating over 400 genes associated with hematological cancers with the ability to detect mutations, translocations and copy number alterations (CNA).[20]

Statistical analysis

Data were summarized as either frequencies and proportions or as medians and ranges. Fisher's exact test and the Wilcoxon rank sum test were employed to assess the correlation between treatment response and high-risk features documented before the initiation of treatment. The distribution for PFS and other time-to-event outcomes were estimated using the Kaplan-Meier procedure. Univariate and multivariate analysis for PFS were performed for known high-risk features using a Cox regression model. Factors associated with a *P* value <0.1 in univariate analysis were included in multivariate analysis if they remained independently associated with outcome at $P<0.05$. We examined the correlation between the NGS-identified genomic features and the likelihood of achieving a CR using Fisher's exact test.

POD24 patients were identified as those who received immunochemotherapy as their initial treatment and experienced progression within 24 months from treatment initiation.[21] We conducted two distinct time-to-event analyses. The initial analysis encompassed all patients experiencing POD24, regardless of when they received the R-len regimen - whether as a second or subsequent line of therapy. In this analysis, the time-to-event commenced at the initiation of R-len treatment. A secondary analysis focused solely on patients for whom R-len was administered as their second line of treatment. Within this subset, outcomes of individuals experiencing POD24 were compared with those having a later relapse at >24 months using the Log-rank test. The time-to-event was initiated at POD on first active treatment or 24 months from first active treatment if progression had not occurred by that time.

Associations were considered significant if they achieved a *P* value of <0.05.

Results

Patients

Between June 2013 and April 2023, we treated 84 patients with R/R FL (82%) and MZL (18%). The median age at the

time of treatment initiation was 65 years (range, 39-94). Forty-five percent of patients had a pretreatment FLIPI score of 3-5, 20% had elevated serum lactate dehydrogenase, 23% had a bulky disease (i.e., largest mass diameter ≥7 cm), 37% had disease refractory to their last treatment, while in 24% lymphoma was refractory to rituximab (defined as lack of response or progressive disease [PD] within 6 months of rituximab therapy; Table 1).[10] Twenty-seven (32%) patients would have not fulfilled eligibility criteria for the AUGMENT trial[10] due to rituximab refractoriness (63%), history of previous malignancies (7%) and aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels exceeding three times the institutional upper limit of normal (7%).

At the time of this analysis, patients had received a median of 9 cycles of lenalidomide (interquartile range [IQR], 6-12), with eight patients receiving more than 12 cycles per the treating physician's decision (see *Online Supplementary Appendix)*. Six patients were still undergoing therapy, 32 completed treatment and 46 discontinued prematurely: 17 patients due to insufficient clinical response (SD/PD); 12 and four patients due to having achieved a CR and partial response (PR) respectively, at cycle 6; five underwent a stem cell transplantation consolidation following initial disease response, and four due to treatment-related toxicity. Other contributing factors included financial toxicity, COVID-19 infection and death for unknown reasons.

Efficacy

The overall response rate (ORR) for the entire cohort, including both partial and complete responses, was 82%, with a best CR rate of 52%. Separately, FL patients showed a best CR rate of 55%, while MZL patients showed a best CR rate of 40%. Among the 76 patients who completed the intended treatment program, 39 (51%) had a CR and 11 (14%) a PR. The trajectory of responses, from treatment initiation to the last assessment, is visually represented in Figure 1. All patients who achieved an interim CR at first response assessment were still in CR at the last assessment. Additionally, of the 44 patients with CR as a best response, all but one maintained it at the EOT. In contrast, patients whose lymphoma exhibited PR (N=39) as initial response demonstrated varied outcomes at the EOT, with 33% ultimately achieving CR, 28% maintaining PR, and 31% having PD.

There were no significant correlations between pretreatment features and the probability of achieving a CR (see Table 2). However, when analyzing the same endpoint in patients with FL and MZL separately, a disease refractory to the last line of therapy was significantly associated with a lower likelihood of achieving a CR in MZL patients (P=0.03). Likewise, harboring bulky disease showed a trend towards a lower likelihood of achieving a CR in MZL patients (P=0.1; *Online Supplementary Table S1*).

We next examined the relationship between genomic features and response. Twenty-five FL patients had NGS data

Table 1. Patient characteristics.

Characteristic	All Patients[1] N=84	Patients with FL[1] N=69	Patients with MZL[1] N=15	P[2]
Age in years ≤60 >60	 29 (35) 55 (65)	 24 (35) 45 (65)	 5 (33) 10 (67)	>0.9
Stage 1/2 3/4	 11 (13) 73 (87)	 11 (16) 58 (84)	 0 (0) 15 (100)	0.2
Elevated LDH	17 (20)	13 (19)	4 (27)	0.5
FLIPI 0-2 3-5	 46 (55) 38 (45)	 40 (58) 29 (42)	 6 (40) 9 (60)	0.3
Bulky disease	19 (23)	15 (22)	4 (27)	0.7
Number of previous lines	2 (1-3)	2 (1-3)	3 (2-5)	0.003
Refractory to rituximab	20 (24)	17 (25)	3 (20)	>0.9
Refractory to last therapy, N=79	29 (37)	24 (37)	5 (36)	>0.9
Reduced lenalidomide dose upfront	14 (17)	13 (19)	1 (7)	0.4
Ineligible for clinical trial	27 (32)	22 (32)	5 (33)	>0.9

[1]Values reported as N (%) or median (interquartile range). [2]Statistical analysis performed using Fisher's exact test and Wilcoxon rank sum test. FL: follicular lymphoma; MZL: marginal zone lymphoma; FLIPI: Follicular Lymphoma International Prognostic Index; LDH: lactate dehydrogenase.

available from tumor samples collected prior to treatment initiation. The association between genomic alterations and the probability of attaining a CR was investigated by considering genes that were altered in at least 20% of the patients (Table 3). There were no significant associations between recurrent genetic alterations and the likelihood of achieving a CR. However, a trend towards lower CR rates (*P*=0.2) was observed in patients harboring *CREBBP* and *TP53* mutations, most of whom did not respond to R-len.

Outcomes

Figure 2 illustrates key survival outcomes after a median follow-up of 22 months (range, 2-111). The median PFS for the entire population was 22 months (95% confidence interval CI: 19-36), and the 2-year PFS rate was 50% (95% CI: 38-66, panel A). The median EFS and OS were 19 months (95% CI: 14-27) and not reached (NR), respectively. At 2 years, the EFS was 43% (95% CI: 32-57), and OS 83% (95% CI: 74-93, panels B and C). The median DoCR was 46 months (95% CI: 22-NR, panel D). Patients who achieved PR as best response exhibited a significantly shorter median duration of response (10 months; 95% CI: 10-23) compared to patients with CR (*P*=<0.001; *Online Supplementary Appendix*). Eleven patients discontinued treatment after completing six cycles upon achieving a CR, due to medical decision in the setting of the COVID-19 pandemic. The median EOT DoCR and 2-year DoCR rate were lower for this subgroup (17 [95% CI: 12-NR] months and 22% ([95% CI: 4-100]) than for patients completing the 12-month program (36 [95% CI: 18-NR) months and 59% ([95% CI: 30-100]; *Online Supplementary Appendix*) though the difference did not meet

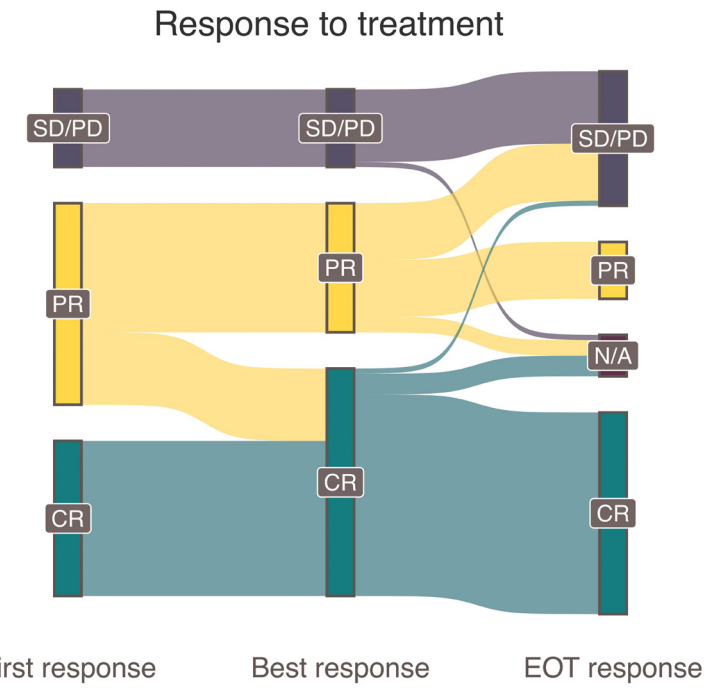

Figure 1. Evolution of responses from treatment start. CR: complete remission; PR: partial remission; SD: stable disease; PD: progressive disease; N/A: not assessed; EOT: end of treatment.

Table 2. Features associated with likelihood of complete remission.

Characteristic	Evaluable Patients[1]	Patients in CR[1]	Patients in PR/SD/PD[1]	*P*[2]
	N=84	N=44	N=40	
Diagnosis				0.4
FL	69 (82)	38 (86)	31 (78)	
MZL	15 (18)	6 (14)	9 (23)	
Age in years				>0.9
≤60	29 (35)	15 (34)	14 (35)	
>60	55 (65)	29 (66)	26 (65)	
Stage				>0.9
1/2	11 (13)	6 (14)	5 (13)	
3/4	73 (87)	38 (86)	35 (88)	
Elevated LDH	17 (20)	7 (16)	10 (25)	0.4
FLIPI				0.7
0-2	46 (55)	23 (52)	23 (58)	
3-5	38 (45)	21 (48)	17 (43)	
Bulky disease	19 (23)	7 (16)	12 (30)	0.2
Number of previous lines	2 (1-3)	2 (1-3)	2 (1-4)	0.3
Refractory to rituximab	20 (24)	8 (18)	12 (30)	0.3
Refractory to last therapy, N=79	29 (37)	13 (30)	16 (44)	0.2
Reduced lenalidomide dose upfront	14 (17)	7 (16)	7 (18)	>0.9
Ineligible for clinical trial	27 (32)	11 (25)	16 (40)	0.2

[1]Values reported as N (%) or median (interquartile range). [2]Statistical analysis performed using Fisher's exact test and Wilcoxon rank sum test. CR: complete remission; PR: partial remission; SD: stable disease; PD: progressive disease; FL: follicular lymphoma; MZL: marginal zone lymphoma; FLIPI: Follicular Lymphoma International Prognostic Index.

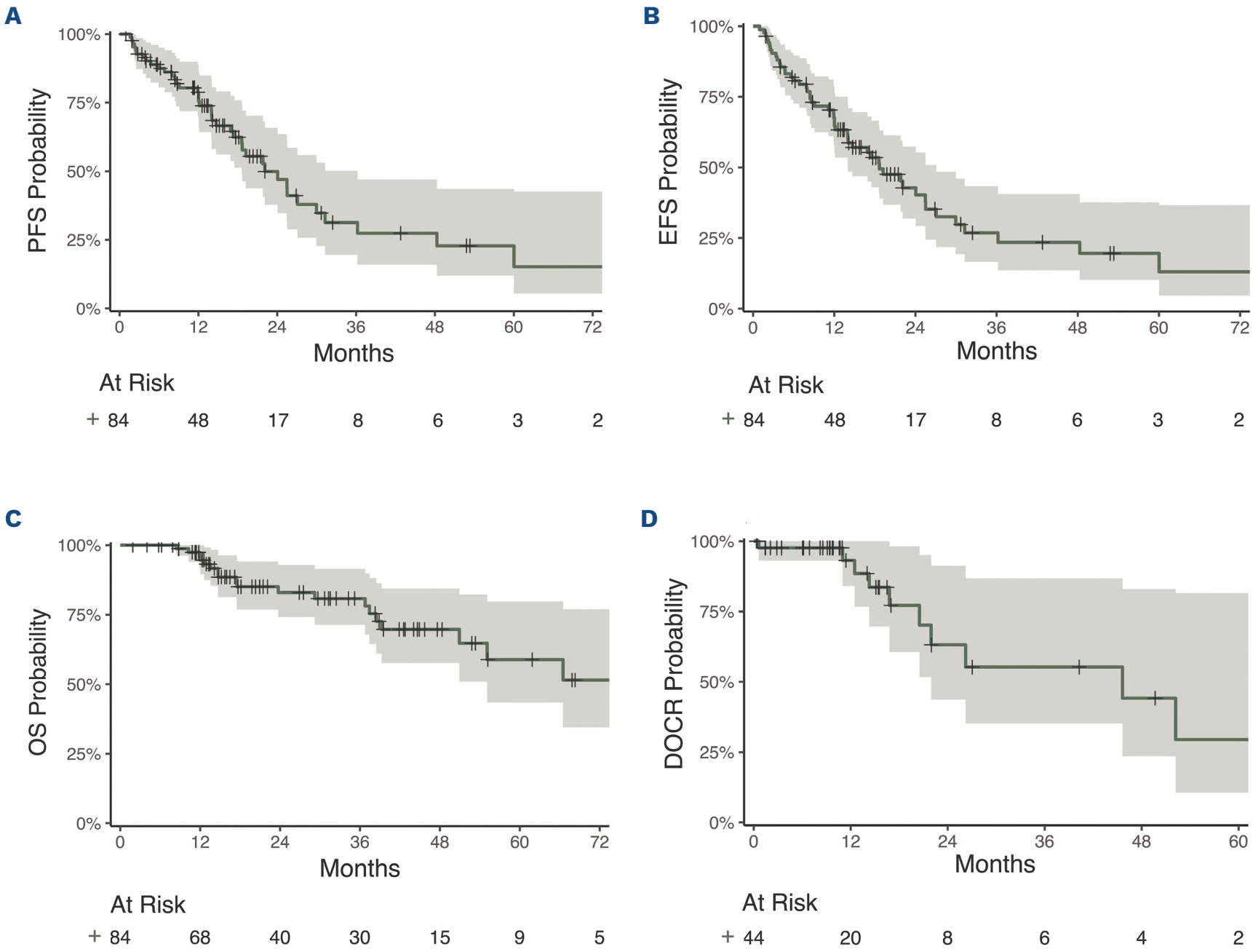

Figure 2. Time-to-event outcomes in patients treated with rituximab-lenalidomide. (A) Progression-free survival (PFS). (B) Event-free survival (EFS). (C) Overall survival (OS). (D) Duration of complete response (DOCR).

Table 3. Best response by genomic alterations in patients with follicular lymphoma.

	CR	PR/SD/PD	*P*[1]	q[2]
	N=13	N=12		
KMT2D			0.8	0.8
Altered	7 (54)	6 (46)		
Non-altered	6 (50)	6 (50)		
CREBBP			0.2	0.4
Altered	5 (38)	8 (62)		
Non-altered	8 (67)	4 (33)		
TNFRSF14			0.8	0.8
Altered	6 (55)	5 (45)		
Non-altered	7 (50)	7 (50)		
EZH2			0.4	0.6
Altered	2 (33)	4 (67)		
Non-altered	11 (58)	8 (42)		
TP53			0.2	0.4
Altered	1 (20)	4 (80)		
Non-altered	12 (60)	8 (40)		

Values are reported as N (%) of altered and non-altered genes. [1]Statistical analysis performed using Fisher's exact test. [2]False discovery rate correction for multiple testing. CR: complete remission; PR: partial remission; SD: stable disease; PD: progressive disease.

statistical significance (*P*=0.5).

Among the 69 patients with FL, the median PFS was 25 months (95% CI: 19-NR) and the 2-year PFS rate was 52% (95% CI: 38-71); the median DoCR was 46 months (95% CI: 22-NR) and the 2-year DoCR was 64% (95% CI: 41-99). Similarly, for the 15 patients with MZL, the median PFS was 22 months (95% CI: 14-NR) and the 2-year PFS was 46% (95% CI, 26-80); the median DoCR was 26 months (95% CI: 21-NR) and the 2-year DoCR was 63% (95% CI: 32-100). Among 48 patients who had first-line chemoimmunotherapy, information about POD24 status was available in 45. Patients with POD24 (N=25) demonstrated a mPFS of 19 months (95% CI: 12-NR), similar to the 17 months (95% CI: 12-NR) observed in non-POD24 patients (N=20). Similar results were observed when considering only patients with a diagnosis of FL (see *Online Supplementary Table S4*). When restricting the analysis to the 23 FL patients who received R-len as second line treatment, individuals with POD24 (N=14) exhibited a shorter mPFS (26 months; 95% CI: 14-NR) than non-POD24 patients (45 months; 95% CI: 28-NR), though this difference did not reach statistical significance (*P*=0.4).

Factors associated with poorer PFS in univariate analysis included rituximab refractoriness, lack of response to the last therapy, and presence of bulky disease. In multivariate analysis, only rituximab refractoriness and bulky disease retained independent negative prognostic value (Table 4).

Safety

The toxicity profile associated with R-len in 84 safety evaluable patients is summarized in Table 5. The most common AE were neutropenia (48%), fatigue (45%), thrombocytopenia (40%), diarrhea (31%), constipation (30%), skin rash (27%), and anemia (19%). Neutropenia and thrombocytopenia were the most common severe toxicities (grade ≥3 in 25% and 4%, respectively). Other AE of special interest included AST/ALT elevation in 12% of patients, peripheral neuropathy in 12%, tumor lysis syndrome in 4% and deep vein thrombosis (DVT) in 5%. Three DVT events occurred in patients receiving anticoagulant therapy and one in a patient receiving antiplatelet therapy. Seventy-four patients (88%) received DVT prophylaxis, 59 in the form of antiplatelet agents, 13 anticoagulants, and two a combination of both. Among those treated with antiplatelet therapy, 52 were prescribed aspirin 81 mg daily, six aspirin 325 mg daily and one clopidogrel 75 mg daily. In the anticoagulant

Table 4. Univariate and multivariate analysis for progression-free survival.

Variable	Univariate[1]		Multivariate[1]	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Stage pretreatment I-II III-IV	 - 1.92 (0.59-6.27)	0.23	 -	 -
Age	0.97 (0.95-1.0)	0.075	-	-
LDH Normal Elevated	 - 1.82 (0.90-3.67)	0.11	 -	 -
FLIPI 0–2 3–5	 - 1.13 (0.60-2.13)	0.71	 -	 -
Bulky disease	2.20 (1.08-4.51)	0.041	2.14 (1.05-4.37)	0.036
Refractory to rituximab	2.37 (1.21-4.66)	0.018	2.32 (1.18-4.54)	0.015
Number of previous lines of therapy 1 ≥2	 - 1.28 (0.65-2.51)	0.46	 -	 -
Refractory to last therapy, N=79 (36 events)	1.98 (1.02-3.81)	0.046	-	-
Reduced lenalidomide dose upfront	0.44 (0.17-1.15)	0.066	-	-
Histology FL MZL	 - 1.52 (0.77-2.97)	0.24	 -	 -
Ineligible for clinical trial	1.81 (0.94-3.47)	0.082	-	-

[1]Statistical analysis performed using Cox regression model. HR: hazard ratio; CI: confidence interval; LDH: lactate dehydrogenase; FL: follicular lymphoma; MZL: marginal zone lymphoma; FLIPI: Follicular Lymphoma International Prognostic Index.

therapy group, eight patients were prescribed apixaban 5 mg twice daily, three rivaroxaban 20 mg daily, one rivaroxaban 15 mg twice daily and one warfarin. Two patients received apixaban in conjunction with aspirin 81 mg and both were affected by atrial fibrillation.

Lenalidomide dose reductions were required in 45 patients, primarily due to neutropenia (22% of cases), impaired renal function, defined as glomerular filtration rate below 60 mL/min (13%), or declining performance status (9%). Other factors included recurrent diarrhea, rash, peripheral neuropathy, thrombocytopenia, anemia, and fatigue. Fourteen patients were treated at a reduced lenalidomide dose upfront due to advanced age or pre-existing conditions considered at high risk for treatment-related toxicity, such as impaired renal function. Four patients permanently discontinued treatment due to severe neutropenia (2 cases), peripheral neuropathy, or colitis (1 case each). No treatment-related deaths occurred.

Discussion

The combination of lenalidomide plus anti-CD20 antibody in patients with iNHL has not been systematically analyzed outside the context of clinical trials in iNHL.[10,11] To the best of our knowledge, this is the first study investigating safety and efficacy of the R-len combination in a real-world context with modern response criteria.[4,18] In our analysis, the ORR was 82% and the best CR rate was 52%. While these results are not directly comparable to those reported by Leonard *et al*. due to different response criteria, we observed somewhat higher response rates.[10] Notably, no factors emerged as significantly associated with response in the whole cohort. However, bulky disease appeared to have a stronger impact on MZL patients, being significantly associated with a lower likelihood of achieving a CR.

Regarding time-to-event outcomes, our analysis revealed a median PFS of 22 months, with a 2-year PFS rate of 50%. While direct comparisons pose challenges, these results parallel those reported in the AUGMENT trial (median PFS of 27 months) despite the presence of patients with rituximab-refractory disease, an exclusion criterion in the AUGMENT trial and a predictor of poorer survival in our analysis.[12] Our PFS analysis on POD24 patients, adhering to the definition of Casulo *et al*.,[21] revealed comparable PFS between POD24 and non-POD24 patients when treated with R-len during second or subsequent treatment lines, aligning with findings the AUGMENT trial.[22] Focusing exclusively on patients receiving the R-len regimen in the second line, we observed a longer median PFS for non-POD24 patients (45 months; 95% CI: 28-NR). It is important to note that the difference with POD24 patients in this setting was not statistically significant, and the sample size was too small to draw definitive conclusions. It is plausible, however, that the prognostic value of POD24 is more relevant in the second line than in later lines, where multiple treatments may select for different mechanism of resistance.[21]

To our knowledge, this is the first study to examine the correlation between pretreatment genomic characteristics and disease responses using a validated NGS panel.[20] This

Table 5. Adverse events.

Adverse event	All grades[1]	Grade 3-4[1]
Neutropenia	40 (48)	21 (25)
Fatigue	38 (45)	-
Thrombocytopenia	34 (40)	3 (4)
Diarrhea	26 (31)	-
Constipation	25 (30)	-
Rash	23 (27)	-
Anemia	16 (19)	2 (2)
Muscle cramps	11 (13)	-
Transaminitis	10 (12)	-
Peripheral neuropathy	10 (12)	1 (1)
Nausea	9 (11)	-
Bilirubin increased	5 (6)	-
UTI	4 (5)	1 (1)
Arthralgia	4 (5)	-
DVT	4 (5)	-
Anorexia	4 (5)	-
ALP increased	3 (4)	-
Headache	3 (4)	-
Tumor lysis syndrome	3 (4)	3 (4)
Dry cough	3 (4)	-
Pneumonia	3 (4)	-
URI	3 (4)	-
Bronchitis	2 (2)	-
Pruritus	2 (2)	-
Soft tissue infection	2 (2)	-
Febrile neutropenia	1 (1)	1 (1)
Bacterial sepsis	1 (1)	1 (1)
Colitis	1 (1)	1 (1)
Abdominal pain	1 (1)	-
Xerosis	1 (1)	-
Bone pain	1 (1)	-
Tremors	1 (1)	-
Shingles	1 (1)	-

[1]Values reported as N (%). Grading according to the CTCAE version 5. ALP: alkaline phosphatase; UTI: urinary tract infection; DVT: deep vein thrombosis; URI: upper respiratory tract infection.

panel analyzed mutations, translocations, and CNA in over 400 genes associated with hematologic malignancies. We did not find any significant associations between the most frequently mutated genes in FL patients and CR rates. Although the sample size is too small to draw definitive conclusions, *CREBBP* and *TP53* mutations showed a trend towards treatment resistance (P=0.2).

Mutations in chromatin-modifying genes have emerged as a defining characteristic of FL,[23] with *CREBBP* mutations being among the most frequent ones.[24,25] *CREBBP* loss of function contributes to lymphomagenesis by promoting immune escape *in vitro* and *in vivo*.[26] It can be hypothesized that lenalidomide's therapeutic effects, which partly rely on enhancing the cytotoxic activity of natural killer cells and T cells, may be hindered by an immune-suppressed tumor microenvironment. However, this observation is speculative and requires confirmation. As for *TP53* mutation, its role in driving lenalidomide resistance is well described in multiple myeloma and myelodysplastic syndromes,[27-29] although the same impact in FL patients warrants further investigation.

Taking into account the retrospective nature of this study and the challenges of accurately assessing non-laboratory-based AE outside of a clinical trial, we did not observe new safety signals with the real-life use of R-len. We observed a relatively lower incidence of grade 3-4 neutropenia compared to clinical trials, possibly attributable to aggressive growth factor support and proactive dose adjustments. Instances of DVT were rare, suggesting that both antiplatelet and anticoagulant prophylaxis were effective in mitigating the risk. The selection of the optimal thrombo-prophylactic agent should be tailored to the patient's profile, and in the absence of significant contraindications the use of aspirin 81 mg daily seems appropriate.

This study has several limitations, primarily due to its retrospective nature and the single-center design. Nonetheless, our results confirm the efficacy and safety profile of combined R-len and support its use as comparator in ongoing registration-directed clinical trials.

Disclosures

ZE-P has received honoraria from OncLive, WebMD; has received research funding from Viracta, Kymera and Amgen. PG has consulted for AstraZeneca, Pharmaceuticals, Kyowa Hakko Kirin and Secura Bio; has received research funding from Kite. PH has consulted for ADC Therapeutics. JL has consulted for OncLive and Merck. AN received research funding from Rafael Pharma and Pharmacyclics; has consulted for Pharmacyclics, Medscape, Targeted Oncology, Morphosys, Pharmacyclics and Janssen; received research funding from NIH. SH has received research funding from Millenium, Seattle Genetics, Crispr Therapeutics, Verastem/SecuraBio, ADC Therapeutics, Takeda, Kyowa Hakko Kirin, Affimed, Trillium Therapeutics and Celgene; has consulted for Trillium Therapeutics, Tubulis, Abcuro Inc., Auxilius Pharma, Cimieo Therapeutics, Daiichi Sankyo, Kyowa Hakko Kirin, ONO Pharmaceuticals, SecuraBio, Shoreline Biosciences, Takeda and Yingli Pharma Ltd. WJ has consulted for Myeloid Therapeutics. AK has received research funding from Celgene, Seattle Genetics, Adaptive Biotechnologies, Genentech, Abbvie Pharmaceuticals, Loxo/Lily Oncology, Astra Zeneca, Pharmacyclics and Beigene; is a current equity holder in publicly-traded company for BridgeBio; has consulted for Astra Zeneca, Loxo/Lily Oncology, Janssen, Genentech and Kite Pharma. AM has received honoraria from Merck, Seattle Genetics; has received research funding from Bristol-Myers Squibb, Merck, Seattle Genetics, Beigene, Incyte and ADC Therapeutics. MLP has received honoraria from Smart Immune, Cellectar, Seres Therapeutics, Rheos, Juno, Ceramedix, Pluto Immunotherapeutics, Novartis, Garuda Therapeutics, MustangBio, Thymofox, Kite, BMS and Synthekine. PT has consulted for Lilly USA, TG Therapeutics, Seagen, Genmab, Genentech and ADC Therapeutics. AZ has received honoraria from AstraZeneca, Janssen Pharmaceuticals, F. Hoffmann-La Roche Ltd, Pharmacyclics, Gilead, BMS and MEI Pharma Inc; has consulted for AstraZeneca, F. Hoffmann-La Roche Ltd, Janssen Pharmaceuticals, Pharmacyclics, Gilead, BeiGene, BMS and MEI Pharma Inc; has received research funding from Abbvie, F. Hoffmann-La Roche Ltd, Gilead and MEI Pharma Inc; has membership on an entity's board of directors or advisory committees for Lymphoma Research Foundation. GS has consulted for AbbVie, Nurix, Orna, EPIZYME, ATB Therapeutics, Ipsen, Nordic Nanovector, F. Hoffmann-La Roche Ltd, Kite/Gilead, Debiopharm, Loxo/Lilly, Genentech, BMS/Celgene, Genmab, Janssen, Incyte, Merck, BeiGene, Molecular Partners and Novartis; has received honoraria for AbbVie and Merck; has received research funding from Janssen, F. Hoffmann-La Roche Ltd and Ipsen; is a current holder of stock options in a privately-held company for Owkin. LF has served on advisory boards for ADC Therapeutics, Seagen, AstraZeneca, Ipsen, Abbvie and Genetech; has consulted for and received honoraria from Genmab, Abbvie and Genetech; has consulted for and received research funding from Genmab, Roche, Abbvie, Genetech and Innate Pharma; has consulted for Evolveimmune; has received travel reimbursement from Genmab and Abbvie. ED, MO, II, PC, AI, CO have non conflicts of interest to disclose.

Contributions

GC and LF conceived the study. GC and LF performed the literature search. GC and AR-D performed data extraction. ED performed statistical analysis. II and PG performed the histologic review. LF and GS provided guidance on the methodology. All authors edited the manuscript and approved the final version of the article.

Funding

Memorial Sloan Kettering Cancer Center is supported by core grant P30 CA008748 funded by the National Cancer

Institute. GC was supported by Associazione italiana contro le leucemie-linfomi e mieloma Milano e Provincia ONLUS. AR-D was supported by a grant from Fundación Española de Hematología y Hemoterapia.

Data-sharing statement

All data reported within the manuscript and further may be available upon reasonable request to the corresponding author.

References

1. Alaggio R, Amador C, Anagnostopoulos I, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms. Leukemia. 2022;36(7):1720-1748.
2. Teras LR, Desantis CE, Cerhan JR, et al. 2016 US lymphoid malignancy statistics by World Health Organization subtypes. CA Cancer J Clin. 2016;66(6):443-459.
3. Dreyling M, Ghielmini M, Rule S, et al. Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2021;32(3):298-308.
4. Zucca E, Arcaini L, Buske C, et al. Marginal zone lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2020;31(1):17-29.
5. Jacobsen E. Follicular lymphoma: 2023 update on diagnosis and management. Am J Hematol. 2022;97(12):1638-1651.
6. Cheah CY, Seymour JF. Marginal zone lymphoma: 2023 update on diagnosis and management. Am J Hematol. 2023;98(10):1645-1657.
7. Hernandez-Ilizaliturri FJ, Reddy N, Holkova B, Ottman E, Czuczman MS. Immunomodulatory drug CC-5013 or CC-4047 and rituximab enhance antitumor activity in a severe combined immunodeficient mouse lymphoma model. Clin Cancer Res. 2005;11(16):5984-5992.
8. Wu L, Adams M, Carter T, et al. Lenalidomide enhances natural killer cell and monocyte-mediated antibody-dependent cellular cytotoxicity of rituximab-treated CD20+ tumor cells. Clin Cancer Res. 2008;14(14):4650-4657.
9. Gribben JG, Fowler N, Morschhauser F. Mechanisms of action of lenalidomide in B-cell non-Hodgkin lymphoma. J Clin Oncol. 2015;33(25):2803-2811.
10. Leonard JP, Trneny M, Izutsu K, et al. AUGMENT: a phase III study of lenalidomide plus rituximab versus placebo plus rituximab in relapsed or refractory indolent lymphoma. J Clin Oncol. 2019;37(14):1188-1199.
11. Morschhauser F, Le Gouill S, Feugier P, et al. Obinutuzumab combined with lenalidomide for relapsed or refractory follicular B-cell lymphoma (GALEN): a multicentre, single-arm, phase 2 study. Lancet Haematol. 2019;6(8):e429-e437.
12. Leonard JP, Trneny M, Offner F, et al. Five-year results and overall survival update from the phase 3 randomized study augment: lenalidomide plus rituximab (R2) vs rituximab plus placebo in patients with relapsed/refractory indolent non-Hodgkin lymphoma. Blood. 2022;140(Suppl 1):561-563.
13. Lansigan F, Andorsky DJ, Coleman M, et al. Completed induction phase analysis of Magnify: phase 3b study of lenalidomide + rituximab (R 2) followed by maintenance in relapsed/refractory indolent non-Hodgkin Lymphoma. Blood. 2021;138(Suppl 1):812.
14. FDA approves lenalidomide for follicular and marginal zone lymphoma | FDA. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-lenalidomide-follicular-and-marginal-zone-lymphoma Accessed March 19, 2024.
15. Falchi L, Morschhauser F, Linton K, et al. EPCORE FL-1: phase 3 trial of subcutaneous epcoritamab with rituximab and lenalidomide (R 2) vs R 2 alone in patients with relapsed or refractory follicular lymphoma. Blood. 2023;142(Suppl 1):3053.
16. Salles G, Park SI, Phillips TJ, et al. Tazemetostat in combination with lenalidomide and rituximab in patients with relapsed/refractory follicular lymphoma: updated phase 1b results of symphony-1 with 22.5 months follow-up. Blood. 2023;142(Suppl 1):3035.
17. Nastoupil LJ, Morschhauser F, Scholz CW, et al. CELESTIMO: A phase III trial evaluating the efficacy and safety of mosunetuzumab plus lenalidomide versus rituximab plus lenalidomide in patients with relapsed or refractory follicular lymphoma who have received ≥1 line of systemic therapy. J Clin Oncol. 2022;40(Suppl 16):TPS7588.
18. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of hodgkin and non-hodgkin lymphoma: The Lugano Classification. J Clin Oncol. 2014;32(27):3059-3067.
19. Cancer Institute N. Common Terminology Criteria for Adverse Events (CTCAE) v5.0. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf Accessed August 9, 2024.
20. Ptashkin RN, Ewalt MD, Jayakumaran G, et al. Enhanced clinical assessment of hematologic malignancies through routine paired tumor and normal sequencing. Nat Commun. 2023;14(1):1-16.
21. Casulo C, Byrtek M, Dawson KL, et al. Early relapse of follicular lymphoma after rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone defines patients at high risk for death: an analysis from the National LymphoCare Study. J Clin Oncol. 2015;33(23):2516-2522.
22. Leonard J, Trneny M, Izutsu K, et al. Augment phase III study: lenalidomide/rituximab (R2) improved efficiacy over rituximab/placebo in relapsed/refractory follicular patients irrespective of POD24 status. Hematol Oncol. 2019;37(Suppl 2):114-115.
23. Green MR. Chromatin modifying gene mutations in follicular lymphoma. Blood. 2018;131(6):595-604.
24. Amin R, Braza MS. The follicular lymphoma epigenome regulates its microenvironment. J Ecp Clin Cancer Res. 2022;41(1):1-7.
25. Schroers-Martin JG, Soo J, Brisou G, et al. Recurrent Crebbp mutations in follicular lymphoma appear localized to the committed B-cell lineage. Blood. 2020;136(Suppl 1):30-31.
26. Zhu Y, Wang Z, Li Y, et al. The role of CREBBP/EP300 and its therapeutic implications in hematological malignancies. Cancers (Basel). 2023;15(4):1219.
27. Kortüm KM, Mai EK, Hanafiah NH, et al. Targeted sequencing of refractory myeloma reveals a high incidence of mutations in CRBN and Ras pathway genes. Blood. 2016;128(9):1226-1233.
28. Jädersten M, Saft L, Smith A, et al. TP53 mutations in low-risk myelodysplastic syndromes with del(5q) predict disease progression. J Clin Oncol. 2011;29(15):1971-1979.
29. Wei S, Chen X, McGraw K, et al. Lenalidomide promotes p53 degradation by inhibiting MDM2 auto-ubiquitination in myelodysplastic syndrome with chromosome 5q deletion. Oncogene. 2013;32(9):1110-1120.