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

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Contributions:

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

Data sharing statement

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

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 pre-treatment 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 (ORR) 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 (mPFS) was 22 months (95% CI 19-36) and the 2-year overall survival (OS) was 83% (95% CI 74-93). The median duration of CR (DoCR) was 46 months (95% CI 22-NR). Factors associated with shorter PFS in multivariate analysis were bulky disease and rituximab refractoriness.

The most common adverse events (AE) 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 (iNHLs) 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 agents⁷⁻⁹ 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-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 the lenalidomide-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/m² 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 twelve 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 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 criteria¹⁸ 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 transplant 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 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 on pre-treatment 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) was performed.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 univariable analysis were included in multivariable 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 complete response 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 encountering 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 pre-treatment FLIPI score of 3-5, 20% had elevated serum LDH, 23% had a bulky disease (i.e., largest mass diameter ≥ 7 cm), 37% were affected by a disease refractory to their last treatment, while 24% by a lymphoma refractory to rituximab (defined as lack of response or progressive disease, PD, within 6 months of rituximab therapy, table 1).¹⁰ Twenty-seven (32%) of patients receiving R-len would have not fulfilled eligibility criteria for the AUGMENT trial.¹⁰ The main reasons for non-eligibility were rituximab refractoriness (63%), history of previous malignancies (7%) and aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels exceeding 3 times the upper limit of normal (7%).

At the time of this analysis, patients received a median of 9 cycles of lenalidomide (IQ range 6-12), with 8 patients receiving more than 12 cycles per the treating physician's decision (data supplement). Six patients were still undergoing therapy, 32 completed treatment and 46 discontinued prematurely: 17 patients due to insufficient clinical response (SD/PD); 12 and 4 patients due to achieving a CR and partial response (PR) at cycle 6, respectively; 5 underwent a stem cell transplant 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 reason.

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, in 39 cases (51%) the disease went into CR and in 11 (14%) into PR. The trajectory of responses, from treatment initiation to the last assessment, is visually represented in Figure 1. All patients whose disease achieved an interim CR at first response were still in CR at the last assessment. Additionally, of the 44 patients whose disease achieved a CR as a best response, all but one maintained it at the EOT. In contrast, patients whose lymphoma attained a PR (N=39) as initial response demonstrated varied outcomes at the EOT, with 33% ultimately achieving CR, 28% maintaining PR, and 31% having progressive disease.

There were no significant correlations between pre-treatment 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 ($p=0.1$, supplemental table 1).

We next examined the relationship between genomic features and response. Twenty-five FL patients had NGS data 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 for CREBBP and TP53 mutations, with most cases harboring these mutations not responding 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% CI 19-36), and the 2-year PFS rate was 50% (95% CI 38-66). 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 whose disease went into PR as best response exhibited a significantly shorter median duration of response (10 months; 95% CI 10-23) compared to patients with CR ($p<0.001$, supplement). Eleven patients discontinued treatment after completing six cycles upon achieving a CR, due to a medical decision in the setting of the COVID-19 pandemic. The median end-of-treatment 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, data supplement) though the difference did not meet statistical significance ($p=0.5$).

Among the 69 patients with FL, the median PFS was 25 months (19-NR) and the 2-year PFS rate was 52% (38-71); the median DOCR was 46 months (22-NR) and the 2-year DOCR was 64% (41-99). Similarly, for the 15 patients with MZL, the median PFS was 22 months (14-NR) and the 2-year PFS was 46% (26-80); the median DOCR was 26 months (21-NR) and the 2-year DOCR was 63% (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 Supplemental Table 4). 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 progression-free survival in univariable analysis included rituximab refractoriness, lack of response to the last therapy, and presence of bulky disease. In multivariable 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 adverse events (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 2 a combination of both. Among those treated with antiplatelet therapy, 52 were prescribed aspirin 81 mg daily, 6 aspirin 325 mg daily and one clopidogrel 75 mg daily. In the anticoagulant therapy group, 8 patients were prescribed apixaban 5 mg twice daily, 3 rivaroxaban 20 mg daily, 1 rivaroxaban 15 mg twice daily and 1 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 (GFR) 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 pre-existing conditions considered at high risk for treatment-related toxicity, such as impaired renal function or advanced age. 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 mPFS 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 (mPFS 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 mPFS for non-POD24 patients (45 months; 95% CI 28-NR). It's 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 pre-treatment genomic characteristics and disease responses using a validated NGS panel.²⁰ This panel analyzed mutations, translocations, and CNAs 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 (CMG) 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 (NK) cells and T cells, may be hindered by an immune-suppressed tumor microenvironment. However, this is purely speculative and requires further confirmation. As for TP53 mutation, it is well described its role in multiple myeloma and myelodysplastic syndromes in driving lenalidomide-resistance,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 AEs 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, indicating 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 we recommend the use of aspirin 81 mg daily.

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 lenalidomide and rituximab and support its use as comparator in ongoing registration-directed clinical trials.

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Table 1 Patients characteristics

Characteristic	All Patients ¹	Patients with FL ¹	Patients with MZL ¹	p-value ²
	N = 84	N = 69	N = 15	
Age				>0.9
Age ≤ 60	29 (35)	24 (35)	5 (33)	
Age > 60	55 (65)	45 (65)	10 (67)	
Stage pre-treatment				0.2
1/2	11 (13)	11 (16)	0 (0)	
3/4	73 (87)	58 (84)	15 (100)	
Elevated LDH	17 (20)	13 (19)	4 (27)	0.5
FLIPI				0.3
0-2	46 (55)	40 (58)	6 (40)	
3-5	38 (45)	29 (42)	9 (60)	
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*
Rituximab refractory	20 (24)	17 (25)	3 (20)	>0.9
Refractory to last therapy³	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

Abbreviations: FL indicates follicular lymphoma; MZL, marginal zone lymphoma; FLIPI, follicular lymphoma international prognostic index

¹ Values reported as n (%) or median (IQ range)

² Statistical analysis performed using Fisher's exact test and Wilcoxon rank sum test

³ Data available on 79 patients

Table 2 Features associated with likelihood of CR

Characteristic	Evaluable Patients ¹ N = 84	Patients in CR ¹ N = 44	Patients in PR/SD/PD ¹ N = 40	p-value ²
Diagnosis				0.4
FL	69 (82)	38 (86)	31 (78)	
MZL	15 (18)	6 (14)	9 (23)	
Age				>0.9
Age ≤ 60	29 (35)	15 (34)	14 (35)	
Age > 60	55 (65)	29 (66)	26 (65)	
Stage pre-treatment				>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
Rituximab refractory	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
Trial Ineligibility	27 (32)	11 (25)	16 (40)	0.2

Abbreviations: CR, indicates complete remission; PR, partial remission; SD, stable disease; PD, progressive disease; FL, follicular lymphoma; MZL, marginal zone lymphoma; FLIPI, follicular lymphoma international prognostic index

¹ Values reported as n (%) or median (IQ range).

² Statistical analysis performed using Fisher's exact test and Wilcoxon rank sum test

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

	CR, N=13	PR/SD/PD, N=12	p-value¹	q-value²
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

Table 4 Univariate and multivariate analysis for progression-free survival

Variable	Univariable ¹		Multivariable ¹	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Stage pre-treatment		0.23		
I-II	–			
III-IV	1.92 (0.59–6.27)			
Age	0.97 (0.95–1.0)	0.075		
LDH		0.11		
Normal	–			
Elevated	1.82 (0.90–3.67)			
FLIPI		0.71		
0–2	–			
3–5	1.13 (0.60–2.13)			
Bulky disease	2.20 (1.08–4.51)	0.041	2.14 (1.05-4.37)	0.036*
Rituximab refractory	2.37 (1.21–4.66)	0.018	2.32 (1.18–4.54)	0.015*
Number of previous lines		0.46		
1	–			
≥ 2	1.28 (0.65–2.51)			
Refractory to last therapy line**	1.98 (1.02–3.81)	0.046		
Reduced lenalidomide dose upfront	0.44 (0.17-1.15)	0.066		
Histology		0.24		
FL	–			
MZL	1.52 (0.77–2.97)			
Trial Ineligibility	1.81 (0.94–3.47)	0.082		

Abbreviations: FLIPI, indicates follicular lymphoma international prognostic index

¹ Statistical analysis performed using Cox Regression model

*

** All analyses included the 84 patients with 39 events, except the univariable analysis for “Refractory to last therapy line,” which included 79 patients with 36 events.

Table 5 Adverse events

Adverse Event	All grade¹	Grade 3-4¹
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)	–

Abbreviations: ALP, alkaline phosphatase; UTI, urinary tract infection; DVT, deep vein thrombosis; URI, upper respiratory tract infection

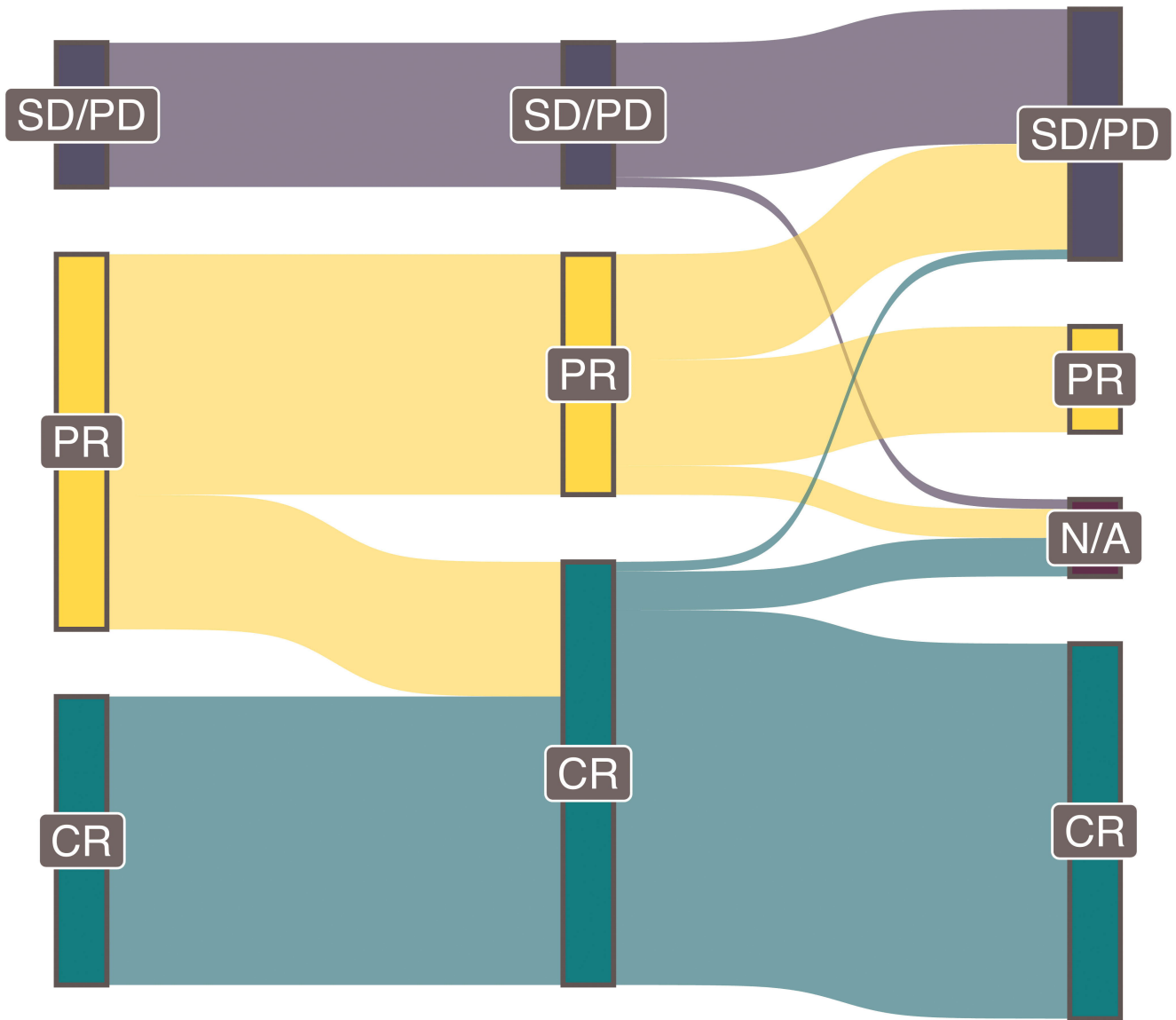
¹ Values reported as n (%). Grading according to the CTCAE version 5

Figure Legend

Figure 1. Evolution of responses from treatment start. Abbreviations: CR, complete remission; PR, partial remission; SD, stable disease; PD, progressive disease. NA, not assessed.

Figure 2. Time to event analyses. Time-to-event outcomes in patients treated with rituximab-lenalidomide. **A:** Progression-free survival. **B:** Event-free survival. **C:** Overall survival. **D:** Duration of complete response

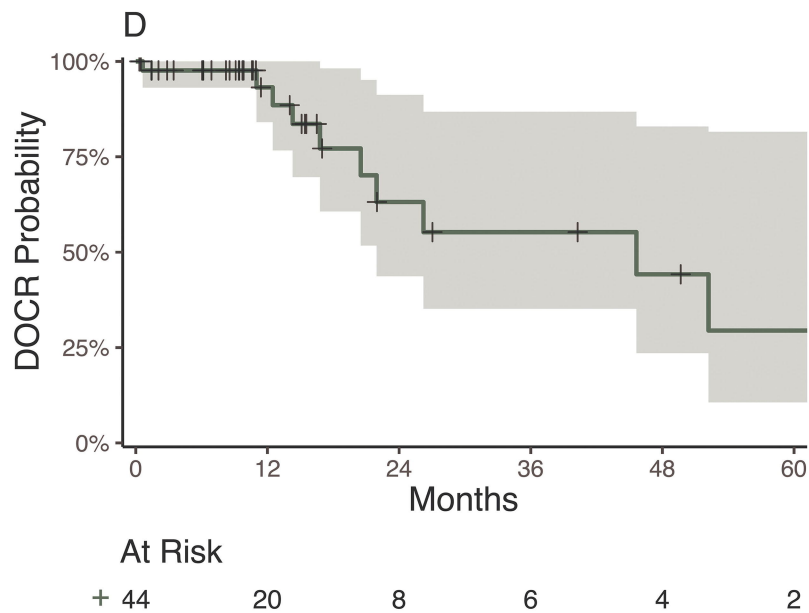
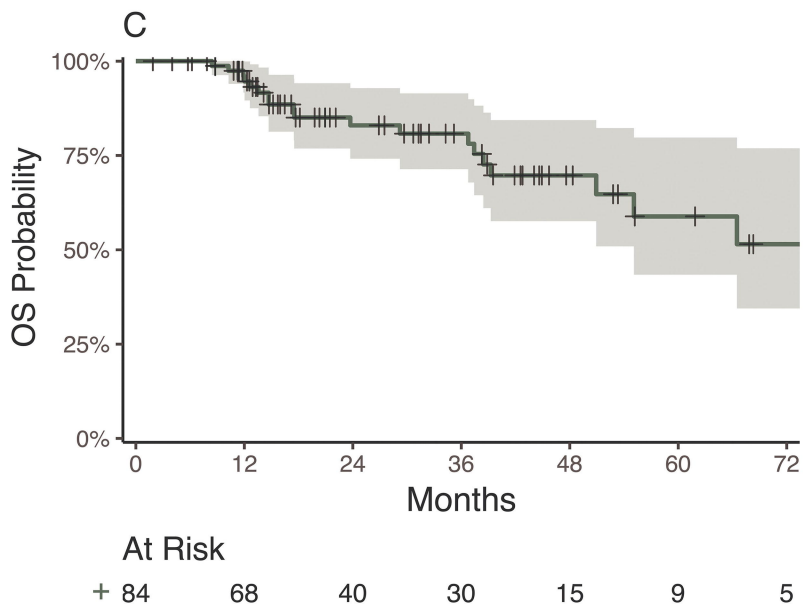
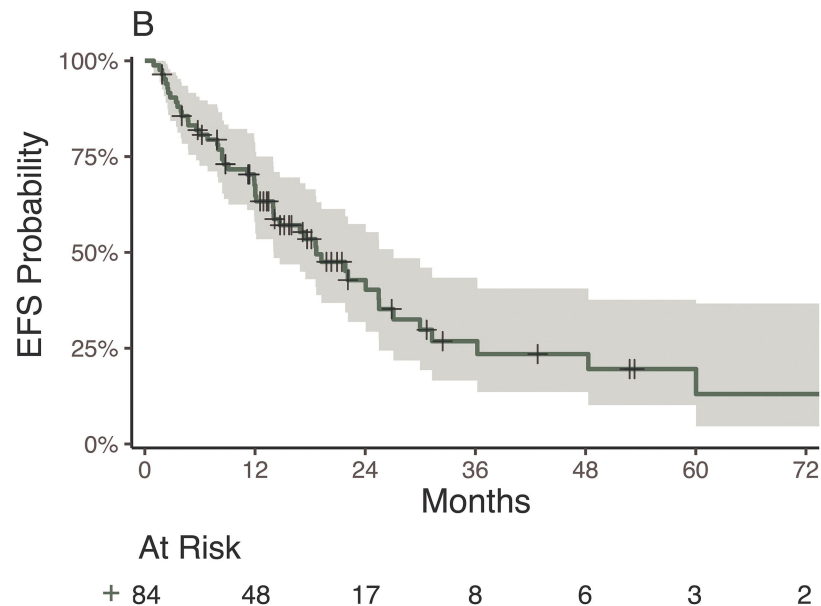
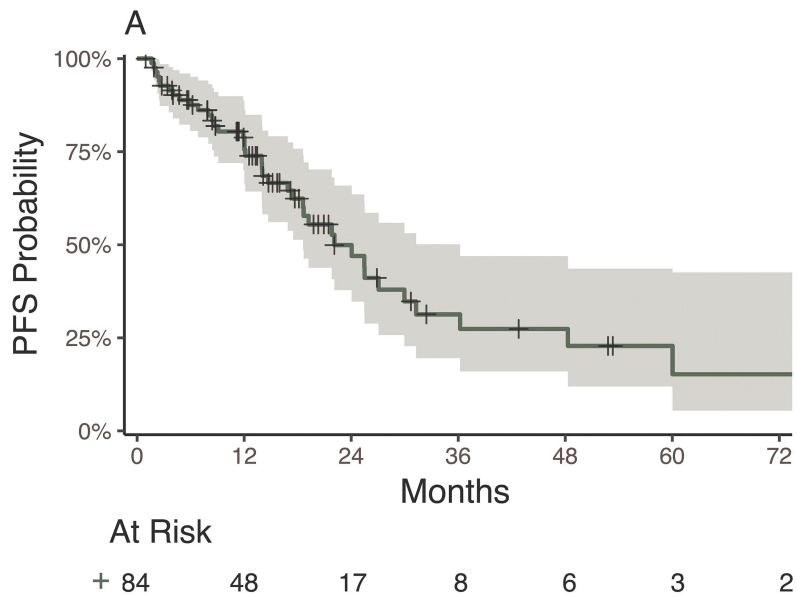
Response to treatment



First response

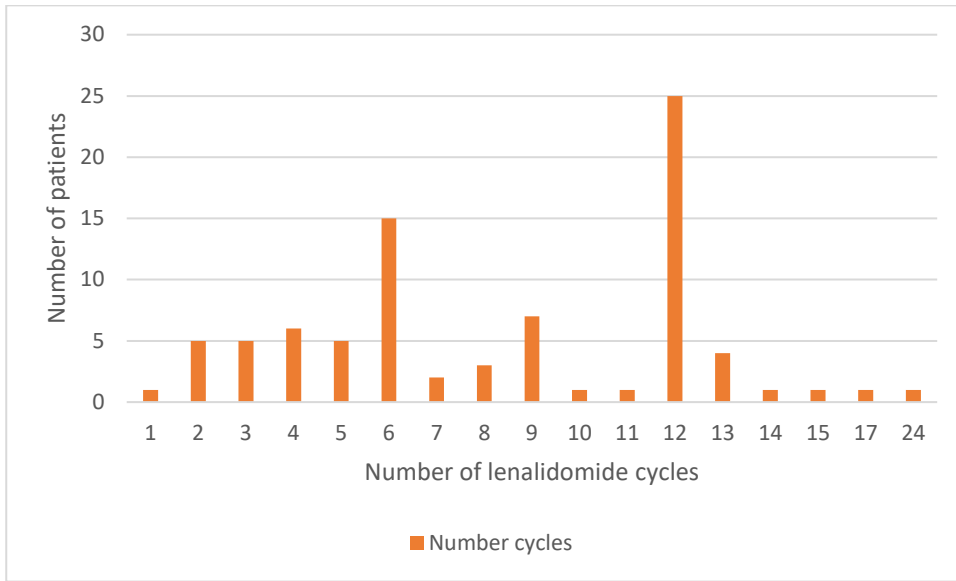
Best response

EOT response



Supplemental Figure 1

Number of lenalidomide cycles received



Supplemental table 1 Patient characteristics stratified by follicular lymphoma (FL)/marginal zone lymphoma (MZL)

Characteristic	FL			MZL		
	CR N = 38 ¹	PR/SD/PD N = 31 ¹	p- value ²	CR N = 6 ¹	PR/SD/PD N = 9 ¹	p- value ²
Age			0.6			0.3
Age ≤ 60	12 (32%)	12 (39%)		3 (50%)	2 (22%)	
Age > 60	26 (68%)	19 (61%)		3 (50%)	7 (78%)	
Number of previous lines	1 (1, 3)	2 (1, 3)	0.5	3 (2, 5)	3 (3, 4)	0.8
Elevated LDH	5 (13%)	8 (26%)	0.2	2 (33%)	2 (22%)	>0.9
FLIPI			0.6			>0.9
0-2	21 (55%)	19 (61%)		2 (33%)	4 (44%)	
3-5	17 (45%)	12 (39%)		4 (67%)	5 (56%)	
Bulky disease	7 (18%)	8 (26%)	0.6	0 (0%)	4 (44%)	0.10
Extranodal involvement	25 (66%)	15 (48%)	0.2	5 (83%)	7 (78%)	>0.9
Rituximab refractory	8 (21%)	9 (29%)	0.6	0 (0%)	3 (33%)	0.2
Refractory to last tx³	13 (35%)	11 (39%)	0.8	0 (0%)	5 (63%)	0.03
Ineligible for clinical trial	10 (26%)	12 (39%)	0.3	1 (17%)	4 (44%)	0.6
Reduced lenalidomide dose upfront	6 (16%)	7 (23%)	0.5	1 (17%)	0 (0%)	0.4
Stage pre-treatment			>0.9			
1/2	6 (16%)	5 (16%)				
3/4	32 (84%)	26 (84%)				
MZL subtype						>0.9
EMZL				1 (17%)	1 (11%)	
NMZL				3 (50%)	6 (67%)	
SMZL				2 (33%)	2 (22%)	

Abbreviations: CR, indicates complete remission; PR, partial remission; SD, stable disease; PD, progressive disease; FL, follicular lymphoma; MZL, marginal zone lymphoma; FLIPI, follicular lymphoma international prognostic index

¹ Values reported as n (%) or median (IQ range)

² Statistical analysis performed using Fisher's exact test and Wilcoxon rank sum test

³ Data available on 79 patients

Supplemental table 2 Duration of Response (DOR) in Responders by Best Response

	N	DOR Events	Median DOR¹	2-year DOR	p-value²
Best Response	69	29			<0.001*
CR	44	10	46 (22–NR)	63% (44–91)	
PR	25	19	10 (10–23)	21% (9–49)	

Abbreviations: NR, not reached; CR, complete remission; PR, partial remission

¹ Values are reported as months (95% CI)

² Statistical analysis performed using Log-rank test.

* p-value significant if <0.05

Supplemental table 3 Duration of Response (DOR) in CR Patients by Timing of CR

	N	DOR Events	Median DOR¹	2-year DOR	p-value²
EOT Response	31	8			0.5
CR after cycle 6	10	4	17 (12–NR)	22% (4–100)	
CR after FTC ³	21	4	36 (18–NR)	59% (30–100)	

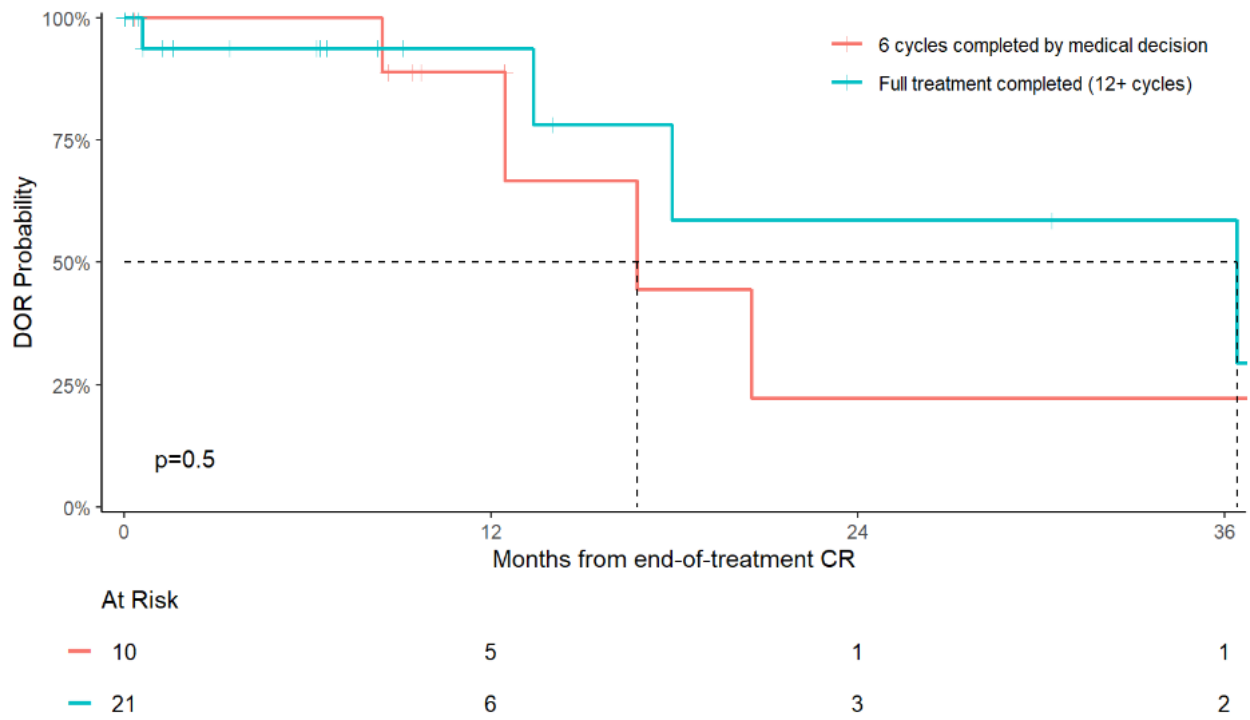
Abbreviations: FTC, full treatment course; NR, not reached; CR, complete remission; EOT, end of treatment

¹ Values are reported as months (95% CI)

² Statistical analysis performed using Log-rank test

³ Patients received 12+ cycles of lenalidomide

Supplemental Figure 2. Duration of end of treatment (EOT) CR by number of treatment cycles



Supplemental table 4 Progression-free survival by POD24

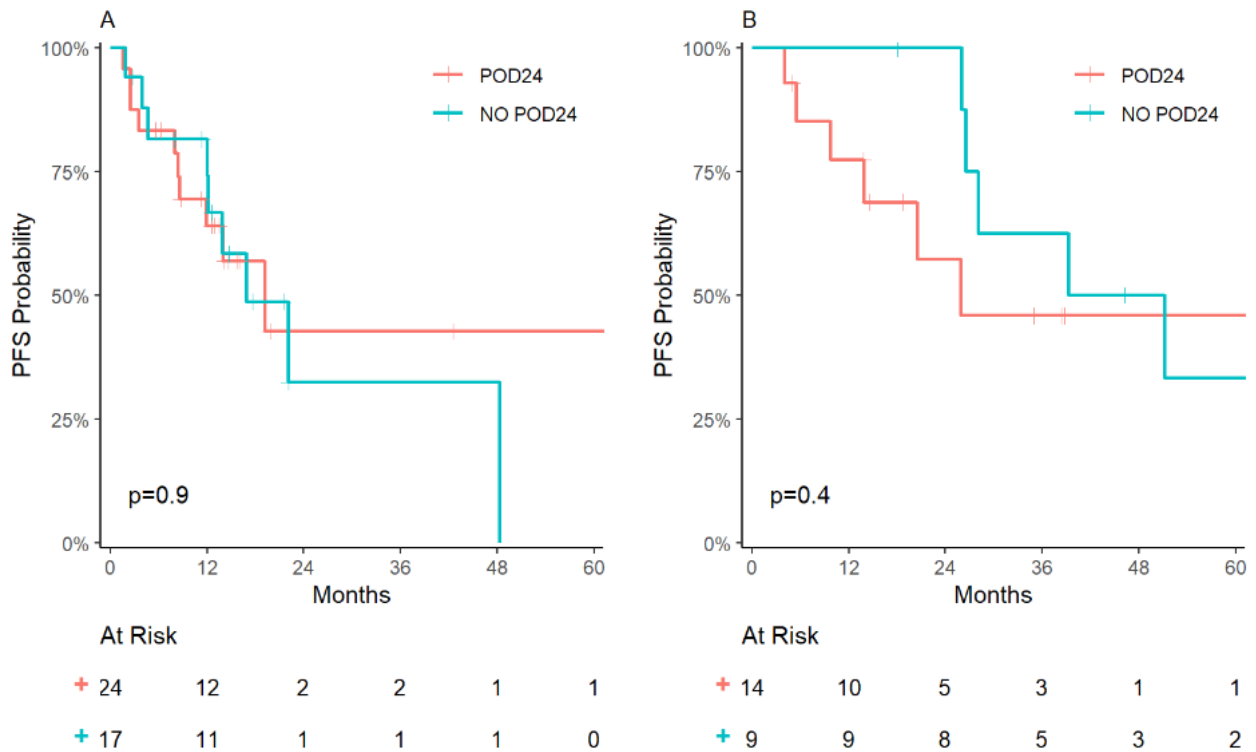
	N	Events	Median PFS¹	2-year PFS	p-value²
All patients receiving CIT as 1st line treatment					0.7
NO POD24	20	11	17 (12–NR)	34% (16–75)	
POD24	25	11	19 (12–NR)	47% (27–83)	
FL patients receiving CIT as 1st line treatment					0.9
NO POD24	17	9	17 (12–NR)	32% (12–87)	
POD24	24	10	19 (12–NR)	43% (21–85)	
FL patients receiving CIT as 1st line and R-len as 2nd line treatment					0.4
NO POD24	9	5	45 (28–NR)	100% (100–100)	
POD24	14	6	26 (14–NR)	57% (34–96)	

Abbreviations: CIT, chemo-immunotherapy; POD24, progression of disease within 24 months of first-line therapy; FL, follicular lymphoma; R-len, rituximab-lenalidomide; NR, not reached; PFS, progression free survival

¹ Values are reported as months (95% CI)

² Statistical analysis performed using Log-rank test

Supplemental Figure 3. Progression-free survival by POD24 status in follicular lymphoma patients



A: Progression-free survival by POD24 status in FL patients who underwent immunochemotherapy as their initial active treatment. Time is measured from the commencement of the rituximab-lenalidomide regimen. **B:** Progression-free survival by POD24 status in FL patients who underwent immunochemotherapy as their initial active treatment and received rituximab-lenalidomide as second active treatment. Time is measured from POD or 24 months from first active treatment.