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Rituximab maintenance after bendamustine-based treatment for follicular lymphoma and mantle cell lymphoma may exert a negative influence on SARS-CoV-2 infection outcomes

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A.S, V.N and P.A conceived the idea and designed the study. A.S, L.L, J.S, E.G, A.L, R.C, A.S, A.J, A.F, T.G, A.S, C.G, M.B, A.C, M.J and A.M supplied study material or patients. A.S, L.L, J.S, E.G, A.L, R.C, A.S, A.J, A.F, T.G, A.S, C.G, M.B, A.C and M.J collected and assembled of data. A.S and V.N performed statistical analysis. A.S, V.N, G.I, F.B and P.A analyzed and interpreted data. A.S, V.N and P.A wrote the manuscript. All autors reviewed and approved the manuscript.

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Different chemoimmunotherapy strategies have been employed as first-line treatment for patients diagnosed with mantle cell lymphoma (MCL) and follicular lymphoma (FL). Cyclophosphamide-based regimens (RCVP/RCHOP) or bendamustine-containing protocols followed by the option of maintenance treatment with an anti-CD20 agent, are the approaches most commonly preferred. We analyzed SARS-CoV-2 infection outcomes in 215 patients diagnosed with FL or MCL treated with chemoimmunotherapy and subsequent rituximab maintenance in 6 tertiary Spanish centers. Of note, temporary interruptions or dose delays during maintenance due to SARS-CoV-2 infection were documented in 44% of patients, with definitive suspension in 22% of patients. Patients receiving maintenance treatment after bendamustine-based regimens presented inferior SARS-CoV-2 infection outcomes compared to patients in maintenance after cyclophosphamide-containing regimens. The former cohort presented higher rates of severe disease, increased hospitalizations and mortality related to the SARS-CoV-2 infection, leading to a shorter overall survival (OS), compared to the cyclophosphamide cohort.

R-CHOP/R-CVP treatment strategies have been widely employed as first-line immunochemotherapy regimens for indolent B-cell non-Hodgkin lymphomas (NHL)[1]. While two randomized clinical trials (Study group indolent Lymphomas, StiL, and BRIGHT) demonstrated enhanced progression-free survival (PFS) and reduced toxicity with bendamustine-rituximab (BR) compared with RCHOP/RCVP[2,3], "real-world" evaluations of the BR approach have shown a trend for increased hospitalizations and infections, albeit without an impact on OS[4]. Moreover, in the GALLIUM study, evaluating the combination of rituximab or obinutuzumab with CHOP, CVP or bendamustine for previously untreated FL patients, a higher rate of infections was reported in the bendamustine arm compared to the CHOP/CVP arm. Also, there was a higher rate of infections in the bendamustine arm, independent of the combination with obinutuzumab or rituximab, and this was particularly evident during the maintenance and follow-up phases. Nevertheless, CHOP was associated with higher rates of grade 3 neutropenia during the induction[5]. Rituximab maintenance (RM) after frontline treatment has significantly improved PFS in FL[6], and both PFS and OS in MCL[7,8]. However, the consensus on the use of RM following frontline BR remains elusive, primarily due to the absence of randomized data demonstrating a clear benefit of RM in this particular setting. While retrospective data suggest the potential safety of RM after BR[9], it has not been systematically evaluated in the context of the SARS-CoV2 pandemic. Published reports have shown that COVID-19 disease presents a high mortality rate in immunocompromised patients, including patients with an active hematologic disease[10,11]. This is particularly evident in

individuals diagnosed with B-cell NHL treated with immunochemotherapy (ICT) including anti-CD20 monoclonal antibodies (MoAbs). In addition, the administration of anti-CD20 moAbs deeply diminishes the seroconversion rate after vaccination[12-15]. The aims of our study were to investigate the incidence and severity of SARS-CoV-2 infection, as well as the seroconversion rate, in patients diagnosed with FL and MCL who were undergoing maintenance after first-line immunochemotherapy treatment based on cyclophosphamide or bendamustine.

In this retrospective analysis, we included all patients diagnosed with FL and MCL who received upfront RCHOP/RCVP or BR and sequential rituximab maintenance (RM) between March 2020 and March 2022 at 6 Spanish centers. Patients included in the study had initiated maintenance therapy during the study period or were already on maintenance by March 2020. This study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Clinical Research Ethics Committee of the Vall d'hebron Institute (Study number: PR(AG)179/2022). An inverse probability of treatment weighting (IPTW) ATE analysis was performed according to the type of first-line treatment (bendamustine or cyclophosphamide-containing regimens) to adjust for potential imbalances in other prognostic variables between both groups in SARS-CoV2 survival (figure 2B) and binary outcomes (figure 1B). A standardized mean difference (SMD) with a threshold of 0.10 was used to assess the balance of covariates between the two groups. COVID-19 disease events were collected from the beginning of RM while COVID-19 disease events before lymphoma onset and during induction therapy were excluded from the analysis. Survival of patients diagnosed with SARS-CoV-2 infection was calculated from the beginning of RM until death by SARS-CoV-2 or last follow-up. The severity of SARS-CoV-2 infection was graded according to the need for either hospitalization or admission to an intensive care unit (ICU). The seroconversion rate was evaluated based on the positivity of spike glycoprotein antibody titers after vaccination within the entire cohort. All statistical analyses were performed using R software version 4.2.2.

The full population included 215 patients, 178 (83%) with FL and 37 (17%) with MCL. Baseline characteristics were analyzed according to the first-line treatment they received (Table 1). In the FL group, 14 (7%) patients were treated with BR induction while 164 (76%) patients had received cyclophosphamide-containing regimens. The MCL cohort included 6 (3%) patients treated with bendamustine and 31 (14%) patients with cyclophosphamide regimens. Median age for the full cohort was 59 years (IQR, 52-68), without significant differences between both groups (62 [bendamustine] vs 59 [cyclophosphamide] years). In the cyclophosphamide group, 8 (4%) patients received RCVP regimen (2 MCL and 6 FL) due to cardiac comorbidities while

187 (96%) received RCHOP. Patients treated with BR received this treatment by the center's choice, and only one patient was given this regimen because of cardiac comorbidities. Response to the first-line of treatment was similar between cohorts, with a complete response rate (CRR) after induction of 80% (bendamustine) vs 77% (cyclophosphamide). Autologous stem cell transplantation (ASCT) was performed in 23 patients (11%), 3 patients with FL and 20 patients with MCL. Following the IPTW analysis, baseline variables, including those associated with an impact on SARS-CoV-2 infection outcomes, such as age, vaccination status and prognostic score (FLIPI or MIPI), were balanced between both groups (SMD <0.1). Response after maintenance was similar between cohorts, with an overall response rate of 100% (bendamustine) vs 84% (cyclophosphamide), p=0.654. Temporary interruptions or dose delays during maintenance due to SARS-CoV-2 infection were reported in 95 (44%) cases and definitive suspensions in 47 (22%) patients. No significant differences in the rate of maintenance delays (55% [bendamustine] vs 43% [cyclophosphamide], p=0.24)] and definitive interruptions (30% [bendamustine] vs 21% [cyclophosphamide], p=0.204) were observed between both groups. SARS-CoV-2 infection was reported in 77 (36%) patients in the full patient population, with a higher rate of infection in the bendamustine group compared to the cyclophosphamide group (60% vs 33%, p=0.026). Thirty-five (16%) patients were hospitalized due to severe COVID-19 disease, and 9 (4%) patients required ICU admission, with higher rates of both endpoints in the bendamustine group, compared to the cyclophosphamide group (53% vs 15% hospitalization episodes, [p<0.001] and 26% vs 2% of ICU admission, [p<0.001]) (figure 1A). These results were also maintained in the IPTW analysis (50% vs 15% hospitalization episodes, [p=0.003] and 26% vs 2% of ICU admission, [p<0.001]) (figure 1B). The severity of SARS-CoV-2 infection was evaluated across different years during the study period, and a sensitivity analysis on the FL cohort was performed (supplementary table 1). In terms of previous vaccination status, 195 (91%) patients had received at least 1 dose of SARS-CoV-2 vaccine, 141 (66%) patients had received 3 or more doses, being mRNA-1273 SARS-CoV-2 the vaccine most frequently used. No differences in vaccination status were observed between both groups in the raw data (85% [bendamustine] vs 92% [cyclophosphamide], p=0.397) or IPTW analysis (87% [bendamustine] vs 92% [cyclophosphamide], p=0.482). The seroconversion rate was 22% in the overall cohort, with no differences according to the type of first-line treatment (35% [bendamustine] vs 21% [cyclophosphamide], p=0.156); these results were confirmed in the IPTW analysis (32% [bendamustine] vs 21% [cyclophosphamide], p=0.315) (figure 1A, 1B). Overall survival according to the induction therapy was determined for the overall cohort. A shorter survival was observed in the bendamustine group, compared to the cyclophosphamide group (HR: 0.2, CI 95% 0.08-0.56; p=0.0019). Regarding the overall survival

of patients diagnosed with SARS-CoV2 infection, a shorter survival was observed in the bendamustine group, compared to the cyclophosphamide group (HR: 0.08, CI 95% 0.02-0.31; p<0.001) (figure 2A); these results were confirmed in the IPTW analysis (HR: 0.11, CI 95% 0.03-0.41; p=0.001) (figure 2B). With a median follow-up of 20.9 months, 36 (17%) patients had relapsed (31 FL and 5 MCL) and 16 patients had died. Regarding patients who received RCVP regimen due to significant cardiac comorbidities, no deaths due to SARS-CoV-2 infection were observed. Among the causes of death, 9 were due to SARS-CoV-2 infection, with significant differences between the bendamustine and cyclophosphamide groups (25% vs 2%, respectively; p<0.001).

In our series, the COVID-19 pandemic significantly affected therapy outcomes in patients diagnosed with FL and MCL, causing treatment delays in 44% and suspensions in 22% of patients receiving rituximab as maintenance treatment. This modification in the maintenance regimen due to SARS-CoV-2 infection, could have an impact on long-term disease control. The previous induction regimen seemed to carry a significant impact on the SARS-CoV-2 infection outcomes, with higher rates of severe disease, hospitalization, ICU admission and death due to COVID-19 disease in the bendamustine group. The depletion and impaired cellular function of CD4+ T cells might have been the cause behind the differences observed between induction therapies, with probably longer T cell suppression impact in the bendamustine group.

Limitations of this report are based on the retrospective nature of data collection. The seroconversion rate was assessed after vaccination but no data regarding antibody status at the time of SARS-CoV-2 infection was available. Moreover, given the lack of a cohort receiving BR induction without sequential RM, we were unable to confirm if the negative impact observed on SARS-CoV-2 infection outcomes in the BR+RM group was due to the bendamustine induction itself or the RM in this particular setting.

In summary, cyclophosphamide-based regimens coupled with rituximab maintenance appeared to be better tolerated in the context of COVID-19 pandemic than bendamustine-rituximab followed by maintenance with this monoclonal antibody. Immunocompromised patients with hematologic malignancies should follow very closely the SARS-CoV-2 vaccination recommendations to decrease the risk of severe infections.

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Variables	Overall N=215	Benda N=20	No benda N=195	SMD	Overall	Benda	No benda	SMD
Age								
Median (IQR)	59 (52-68)	62 (58-73)	59 (52-67)	0.0001	60 (53-63)	60 (53-63)	59 (52-68)	0.0994
Sex								
- F	104 (48%)	9 (45%)	95 (49%)	-0.0750	47%	46%	48%	-0.0194
- M	111 (52%)	11 (55%)	100 (51%)	0.0750	53%	54%	52%	0.0194
Diagnosis								
- MCL	37 (17%)	6 (30%)	31 (16%)	0.3400	17%	18%	17%	0.0096
- FL	178 (83%)	14 (70%)	164 (84%)	-0.3400	83%	82%	83%	-0.0096
Stage								
- I/II	25 (12%)	2 (10%)	23 (12%)	-0.0580	12%	13%	12%	-0.0539
- II/IV	190 (88%)	18 (90%)	172 (88%)	0.0580	88%	87%	88%	0.0539
B symptoms								
- No	179 (83%)	15 (75%)	164 (84%)	-0.2270	81%	77%	84%	-0.0702
- Yes	36 (17%)	5 (25%)	31 (16%)	0.2270	19%	23%	16%	0.0702
ASCT								
- No	192 (89%	19 (95%)	173 (89%)	0.2310	90%	90%	89%	0.011
- Yes	23 (11%)	1 (5%)	22 (11%)	-0.2310	10%	10%	11%	-0.011
Vaccination								
- No	19 (9%)	3 (15%)	16 (8%)	0.2120	11%	13%	8%	0.0513
- Yes	195 (91%)	17 (85%)	178 (92%)	-0.2120	89%	87%	92%	-0.0513
FLIPI/MIPI								
- High	49 (24%)	9 (47%)	40 (21%)	0.2620	24%	25%	24%	-0.0177
- Intermediate	123 (59%)	7 (37%)	116 (61%)	-0.2453	56%	52%	59%	0.0156
- Low	36 (17%)	3 (16%)	33 (17%)	-0.0167	20%	23%	17%	-0.0696
Best Response								
- CR	167 (78%)	16 (80%)	151 (77%)	0.0630	82%	87%	78%	0.0949
- PR	48 (22%)	4 (20%)	44 (23%)	-0.0630	18%	13%	22%	-0.0949

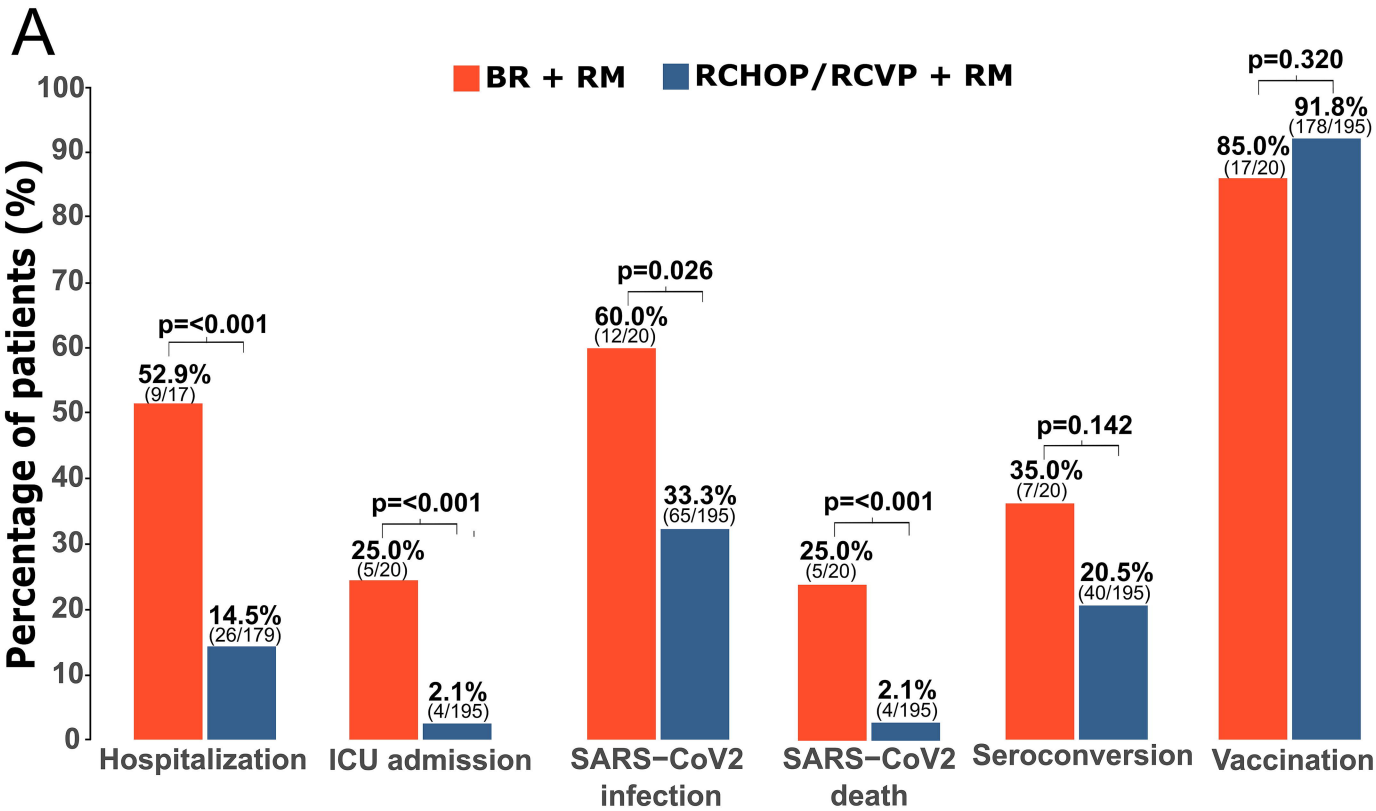
TABLE AND FIGURE LEGENDS

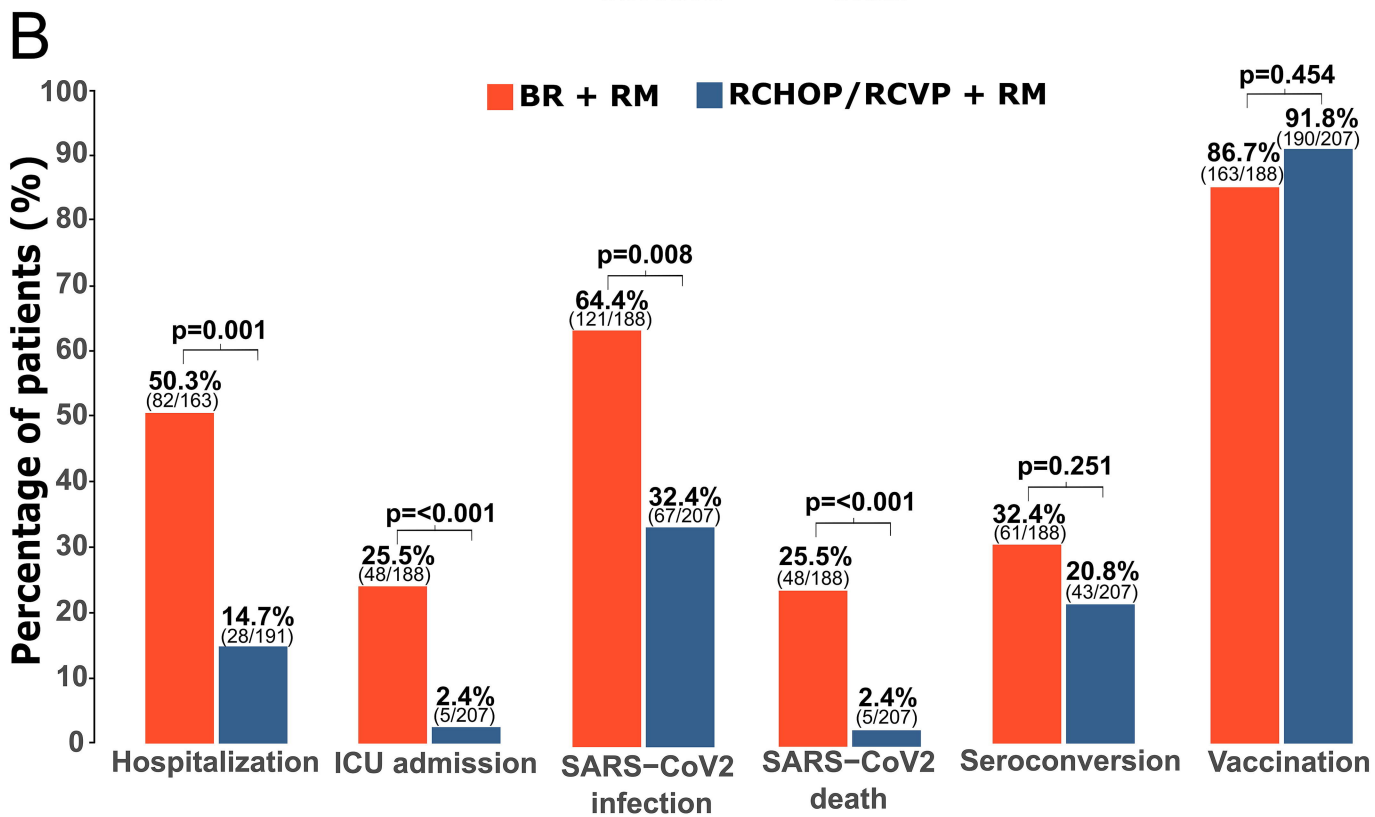
Table 1. Main characteristics of the overall cohort of patients included in the study and an evaluation of these variables using a propensity score analysis based on inverse probability

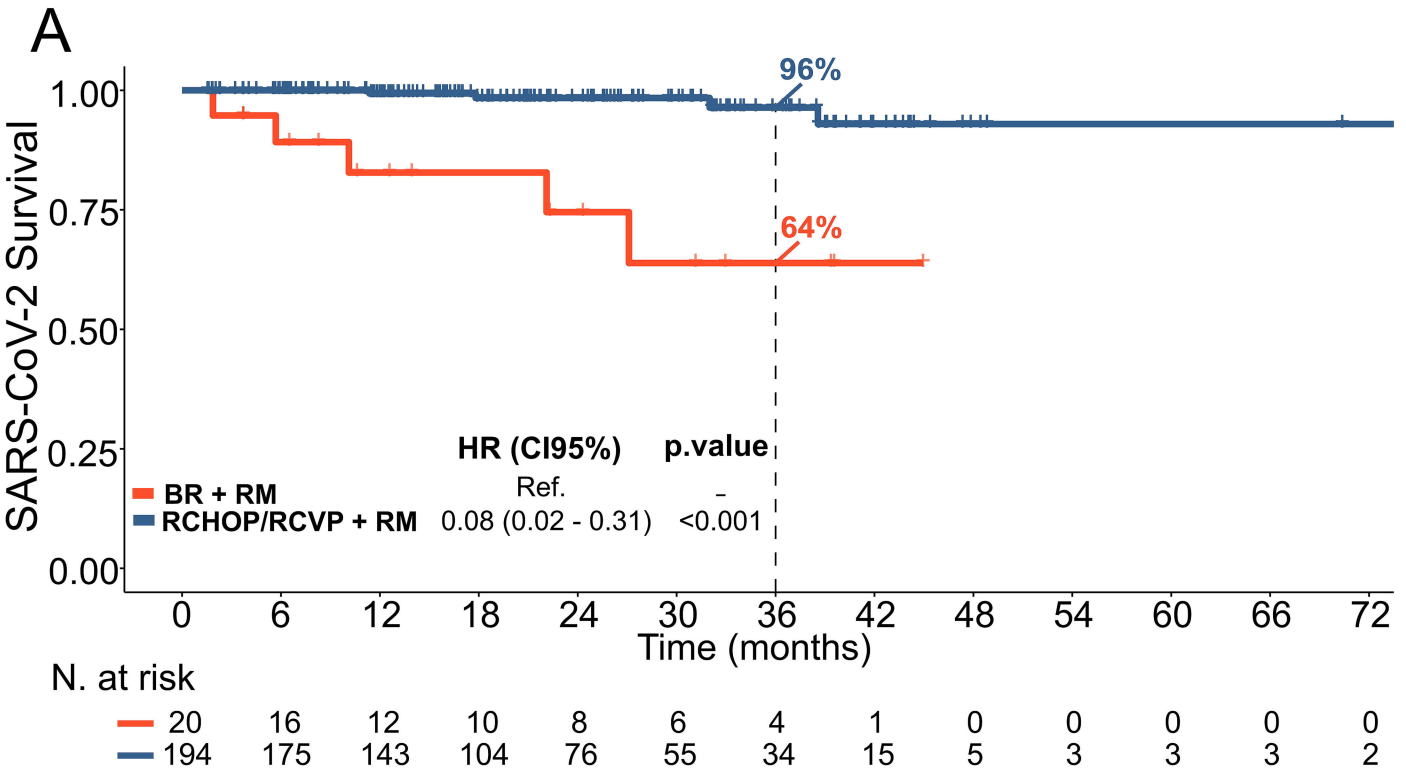
of treatment weighting (IPTW). Benda, bendamustine; F, female; M, male; MCL, mantle cell lymphoma; FL, follicular lymphoma; ASCT, autologous stem cell transplantation; FLIPI, follicular lymphoma international prognostic index; MIPI, mantle cell lymphoma international prognostic index; SMD, standardized mean differences

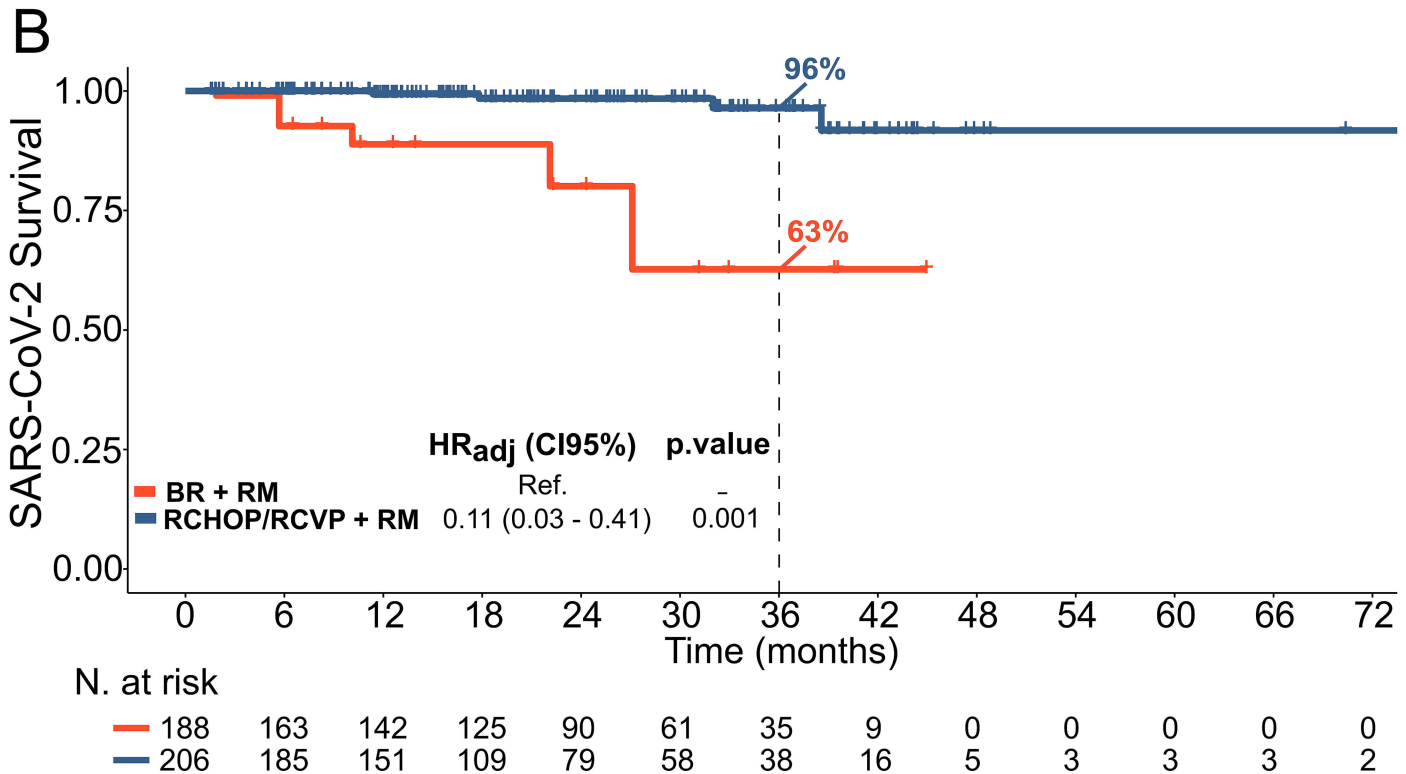
Figure 1. Impact on SARS-CoV-2 infection according to the first-line treatment administered (bendamustine-based vs cyclophosphamide-based strategies). (A) Differences according SARS-CoV-2 infection outcomes of the patients from the total cohort. (B) Differences according SARS-CoV-2 infection outcomes of the patients from the total cohort using a propensity analysis based on inverse probability of treatment weighting (IPTW). BR + RM, bendamustine plus rituximab and rituximab maintenance; RCHOP/RCVP + RM, RCHOP/RCVP and rituximab maintenance; ICU, intensive care unit.

Figure 2. Survival of patients diagnosed with SARS-CoV-2 infection. (A) Survival of the overall cohort of patients included in the study diagnosed with SARS-CoV-2 infection. (B) Survival of patients diagnosed with SARS-CoV-2 infection using a propensity analysis based on inverse probability of treatment weighting (IPTW).


A
BR + RM
RCHOP/RCVP + RM
Percentage of patients (%)
100
90
80
70
60
50
40
30
20
10
0
p=<0.001
52.9%
(9/17)
14.5%
(26/179)
p=<0.001
25.0%
(5/20)
2.1%
(4/195)
p=0.026
60.0%
(12/20)
33.3%
(65/195)
p=<0.001
25.0%
(5/20)
2.1%
(4/195)
p=0.142
35.0%
(7/20)
20.5%
(40/195)
p=0.320
85.0%
(17/20)
91.8%
(178/195)
Hospitalization
ICU admission
SARS−CoV2 infection
SARS−CoV2 death
Seroconversion
Vaccination


B
BR + RM
RCHOP/RCVP + RM
Percentage of patients (%)
100
90
80
70
60
50
40
30
20
10
0
p=0.001
50.3%
(82/163)
14.7%
(28/191)
p=<0.001
25.5%
(48/188)
2.4%
(5/207)
p=0.008
64.4%
(121/188)
32.4%
(67/207)
p=<0.001
25.5%
(48/188)
2.4%
(5/207)
p=0.251
32.4%
(61/188)
20.8%
(43/207)
p=0.454
86.7%
(163/188)
91.8%
(190/207)
Hospitalization
ICU admission
SARS−CoV2 infection
SARS−CoV2 death
Seroconversion
Vaccination


A
SARS-CoV-2 Survival
1.00
0.75
0.50
0.25
0.00
96%
64%
HR (CI95%)
p.value
BR + RM
Ref.
–
RCHOP/RCVP + RM
0.08 (0.02 - 0.31)
<0.001
0
6
12
18
24
30
36
42
48
54
60
66
72
Time (months)
N. at risk
20 16 12 10 8 6 4 1 0 0 0 0 0
194 175 143 104 76 55 34 15 5 3 3 3 2


B
SARS-CoV-2 Survival
1.00
0.75
0.50
0.25
0.00
96%
63%
HRadj (CI95%)
p.value
BR + RM
Ref.
–
RCHOP/RCVP + RM
0.11 (0.03 - 0.41)
0.001
0
6
12
18
24
30
36
42
48
54
60
66
72
Time (months)
N. at risk
188 163 142 125 90 61 35 9 0 0 0 0 0
206 185 151 109 79 58 38 16 5 3 3 3 2

SUPPLEMENTARY DATA

SUPPLEMENTAL TABLE AND FIGURE LEGENDS

Supplementary table 1. Unadjusted and adjusted for Inverse probability treatment weighting (IPTW) results for binary endpoints and survival univariate logistic and Cox models, respectively. Results of unadjusted are presented separately for Follicular Lymphoma (FL) and overall cohort (Mantle Cell Lymphoma (MCL) plus FL). HR represents Hazard Ratio for survival outcomes, while OR denotes Odds Ratio for binary outcomes, p-values indicate statistical significance.

Supplementary table 2. Hospitalization rates among patients diagnosed with SARS-CoV-2 infection in the bendamustine regimen plus rituximab maintenance (BR+RM) group versus RCHOP or RCVP regimen plus rituximab maintenance group (R-CHOP/R-CVP + RM).

Supplementary figure 1. Propensity score building according to an inverse probability treatment weighting (IPTW) ATE analysis. The analyzed variables are included in explanatory.

Supplementary Table 1

		Unadjusted				Adjusted	
		Only FL (n=178)		MCL/FL (n=214)		MCL/FL (n=207)	
		HR/OR (95% CI)	p-value	HR/OR (95% CI)	p-value	HR/OR (95% CI)	p-value
Survival	**SARS-CoV2 Survival**	0.05 (0.01 - 0.25)	<0.001	0.08 (0.02 - 0.31)	<0.001	0.11 (0.03 - 0.41)	0.001
Binary	**Hospitalization**	0.15 (0.04 - 0.52)	0.002	0.15 (0.05 - 0.43)	<0.001	0.17 (0.06 - 0.50)	0.001
	ICU admission	0.03 (0.00 - 0.18)	<0.001	0.06 (0.01 - 0.26)	<0.001	0.07 (0.02 - 0.28)	<0.001
	SARS-CoV2 infection	0.27 (0.08 – 0.83)	0.026	0.33 (0.12 – 0.85)	0.022	0.27 (0.09 – 0.69)	0.008
	SARS-CoV2 death	0.05 (0.00 - 0.24)	<0.001	0.06 (0.01 - 0.26)	<0.001	0.07 (0.02 - 0.28)	<0.001
	Seroconversion	0.56 (0.17 - 2.15)	0.353	0.48 (0.18 - 1.35)	0.142	0.55 (0.20 - 1.63)	0.251
	Vaccination	2.10 (0.30 -8.94)	0.367	1.96 (0.43 - 6.67)	0.320	1.72 (0.32 – 6.25)	0.454

Supplementary Table 2

	BR+RM		R-CHOP/R-CVP + RM	
Year Sars-Cov2 infection	**Hospitalization**	**No hospitalization**	**Hospitalization**	**No hospitalization**
2020	1 (100%)	0 (0%)	5 (71%)	2 (29%)
2021	5 (100%)	0 (0%)	14 (58%)	10 (42%)
2022	3 (50%)	3 (50%)	7 (21%)	27 (79%)

Supplementary Figure 1