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TO THE EDITOR:

Humoral and cellular responses after COVID-19 vaccination in anti-CD20-treated lymphoma patients

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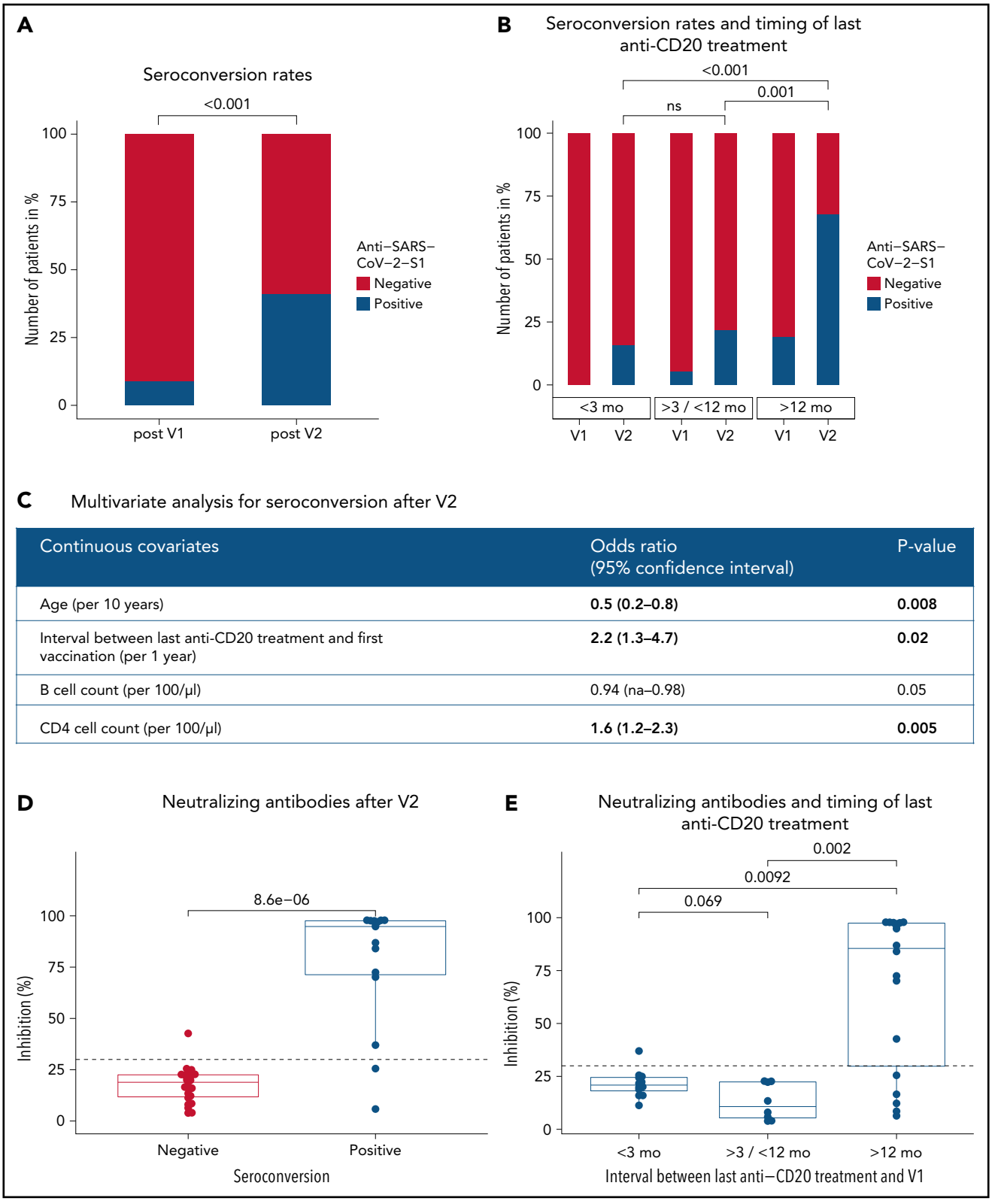
Patients with hematological neoplasms, including lymphoma patients, have a high risk for severe COVID-19 diseases.[1-4] COVID-19 vaccinations induce strong serologic and T-cell responses in immunocompetent humans and thereby effectively prevent severe COVID-19 disease courses.[5-8] There is accumulating evidence that humoral immune responses after vaccination are impaired in patients with hematological malignancies, especially if they were treated with B-cell-depleting therapies such as anti-CD20 antibodies.[9-11] However, there is limited information about the T-cell-mediated vaccine responses after anti-CD20 treatment. In this study, we investigated the humoral and cellular responses after COVID-19 vaccination in lymphoma patients who had received anti-CD20 treatment.



Continuous covariates	Odds ratio (95% confidence interval)	P-value
Age (per 10 years)	**0.5 (0.2–0.8)**	**0.008**
Interval between last anti-CD20 treatment and first vaccination (per 1 year)	**2.2 (1.3–4.7)**	**0.02**
B cell count (per 100/μl)	0.94 (na–0.98)	0.05
CD4 cell count (per 100/μl)	**1.6 (1.2–2.3)**	**0.005**

Figure 1. Humoral responses after COVID-19 vaccination in anti-CD20-treated lymphoma patients. (A) Seroconversion rates after the first and second COVID-19 vaccination (post V1: n = 57, post V2: n = 76). The median time from the first and second vaccination to serology testing was 15 days (IQR: 14–17 days) and 16 days (IQR: 14–24.2 days), respectively. The anti-SARS-Cov-2-S1 antibody response rate after the second vaccination was significantly higher than after the first vaccination (V2 vs V1: 41% [31/76] vs 9% [5/57], McNemar test $P < .001$). A semiquantitative index of <1 was classified as negative, and a value of ≥1 was classified as positive. All patients with an available sample prior to vaccination (n = 70, median sample collection prior to first vaccination: 254 days, IQR: 17–448 days) were tested negatively for anti-SARS-CoV-2-S1 and anti-SARS-CoV-2-N antibodies. (B) Seroconversion rates after the first and second COVID-19 vaccination according to the interval between the last anti-CD20 treatment and first COVID-19 vaccination (<3 months: post V1: n = 17, post V2: n = 19; >3 months and <12 months: post V1: n = 19, post V2: n = 23; >12 months: post V1: n = 21, post V2: n = 34). The seroconversion rate after the second vaccination was significantly increased when the interval between the last

The measurement of anti-SARS-Cov-2-S1 and anti-SARS-CoV-2-N antibody levels was performed as previously described.[12] Patients with a known history of SARS-CoV-2 infection or detected response against the nucleocapsid protein (anti-SARS-CoV-2-N) were excluded from this study. For a subset of patients for whom additional samples were available, we assessed the neutralizing antibody capacity and T-cell responses. A detailed description of data collection and analysis can be found in the supplemental Methods, available on the *Blood* Web site.

Patient characteristics of all 80 patients are summarized in supplemental Table S1. The majority of patients were diagnosed with an aggressive (40%) or an indolent (40%) form of B-cell lymphoma. A smaller cohort of 14% was diagnosed with chronic lymphocytic leukemia. Anti-CD20 treatment (rituximab or obinutuzumab) was combined with chemotherapy or novel agents in 41% and 15% of patients, respectively. Twenty-nine percent of patients were treated with an anti-CD20 monotherapy predominantly as maintenance after immunochemotherapy. Fifty-six percent of patients had received their last anti-CD20 treatment within <12 months prior to COVID-19 vaccination. Vaccines were largely mRNA-based. The median time from the first or second vaccination to serology testing was 15 days (interquartile range [IQR]: 14–17 days) and 16 days (IQR: 14–24.2 days), respectively. Within a median follow-up of 151 days (range 88–239 days) from the first COVID-19 vaccination, no breakthrough infection was reported by patients.

The overall seroconversion rate after 2 vaccination doses, defined as an index of anti-SARS-CoV-2-S1 ≥1, was 41% in our cohort. The seroconversion rate and antibody levels after the second vaccination were significantly higher than after the first vaccination (seroconversion rate: 41% vs 9%, $P < .001$; antibody levels: median [range], 0.2 [0–572] vs 0.09 [0–12], $P = .004$) (Figure 1A). This indicates that at least 2 vaccinations are key in lymphoma patients with anti-CD20 treatment. However, the median antibody levels of patients with seroconversion after the second vaccination (median 67.7, range: 1.6–572) were still remarkably lower than the antibody levels which were reported in healthy mRNA-vaccinated cohorts (116.2).[13] Therefore, studies that investigate the efficacy of booster vaccination in this vulnerable patient cohort are urgently needed.

We aimed to assess which factors contributed to the impaired antibody response after COVID-19 vaccination. The interval between the last anti-CD20 treatment and dosing of the COVID-19 vaccine was positively associated with increasing seroconversion rates. Patients with their last anti-CD20 treatment at least 12 months prior to their first vaccination benefitted most with an overall response (OR) rate of 68% (Figure 1B). In contrast, response rates in patients who had received their last anti-CD20 treatment within 3 months to 12 months or <3 months were decreased with 22% (>12 vs 3 months to 12 months; $P = .001$) and 16% (>12 months vs <3 months; $P < .001$), respectively. We further investigated if antibody response rates were different between patients who received anti-CD20 monotherapy or combination treatment with chemotherapy (supplemental Table S2; supplemental Figure S1). No statistically significant difference was found between these subgroups (anti-CD20 monotherapy 36%, anti-CD20/chemotherapy 56%, $P = .2$). Patients who received anti-CD20 treatment and novel agents (n = 12) or novel agents after failure of anti-CD20 containing treatments (n = 4) had very low seroconversion rates (17% and 0%, respectively). The seroconversion rate after homologous mRNA-based vaccination was 41% (26/67), 0% after non-mRNA-based vaccination (0/2), and 71% after heterologous vaccination (5/7) (supplemental Table S3).

We performed a multivariate analysis which confirmed the interval from the last anti-CD20 treatment to vaccination as an independent predictor and further revealed high CD4 cell counts as an additional independent predictor to develop a serologic response (Figure 1C, univariate analysis; supplemental Table S4).

We further tested antibody neutralization responses and found that 87% of seroconverted patients and 4% of patients without seroconversion had viral neutralization capacities exceeding the cutoff of 30%. The median neutralization capacity in the cohort of seroconverted patients was 95% and was comparable with the neutralization capacities reported in healthy individuals[13] (Figure 1D). As expected, neutralizing antibody capacities followed similar trends as described for seroconversion rates (Figure 1E; supplemental Figure S2).

T-cell responses after COVID-19 vaccination were assessed with an IFNγ ELISpot assay in patients for whom peripheral blood mononuclear cells were available and in 7 fully vaccinated healthy donors (supplemental Table S5). The median time between second vaccination and sample collection was 17 days (IQR 14–21 days) in the vaccinated patient cohort and 18 days (IQR 14–80 days) in the healthy control cohort.

A specific T-cell response after incubation with 2 overlapping peptide pools representing the complete spike protein was evident in 29 out of 50 vaccinated patients (58%) and in 5 out of

Figure 1 (continued) anti-CD20 treatment and first vaccination was >12 months compared with an interval of 3 months to 12 months (68% vs 22%, Fisher's exact test $P = .001$) or <3 months (68% vs 16%, Fisher's exact test $P < .001$). (C) Multivariate logistic regression analysis for seroconversion after the second vaccination in anti-CD20-treated patients (complete case analysis, n = 50). Independent predictors for seroconversion were age (per 10 years, OR 0.5 [95% CI 0.2–0.8], $P = .008$), the interval between last anti-CD20 treatment and first vaccination (per year, OR 2.2 [95% CI 1.3–4.7], $P = .02$), and the CD4 T-cell count (per 100 cells/μL, OR 1.6 [95% CI 1.2–2.3], $P = .005$). (D) SARS-CoV-2 neutralizing capacity of anti-CD20-treated lymphoma patients according to the anti-S1-measured seroconversion. The neutralizing capacity of COVID-19 vaccine-induced antibodies was measured with a SARS-CoV-2 surrogate virus-neutralizing assay. Values were normalized to a negative control, and the inhibition capacity of the SARS-CoV-2 receptor binding domain: angiotensin-converting enzyme 2 interaction was expressed as a percentage. A cutoff of 30% inhibition was applied according to the manufacturer's instructions and indicates the absence of a level of neutralizing antibodies below the limit of detection (represented by the dashed black line). The neutralizing antibody capacity was assessed in a subset of patients for whom additional samples were available (n = 38). Thirteen out of 15 patients (87%) with a positive anti-S1 antibody response had an inhibition exceeding the clinical cutoff for viral neutralization of 30%, whereas 22 out of 23 patients (96%) without seroconversion failed to achieve a successful neutralizing capacity. (E) SARS-CoV-2 neutralizing capacity of anti-CD20-treated lymphoma patients according to the interval between the last anti-CD20 treatment and first COVID-19 vaccination. The median neutralizing capacity after the second vaccination was significantly increased when the interval between the last anti-CD20 treatment and first vaccination was >12 months compared with an interval of 3 months to 12 months (12 months vs 3 months to 12 months: 86% [range 6% to 98%] vs 11% [range 4% to 23%], $P = .002$) or <3 months (12 months vs <3 months: 86% [range 6% to 98%] vs 21% [range 11% to 37%], $P = .009$). V1, vaccination 1; V2, vaccination 2; ns, not significant.

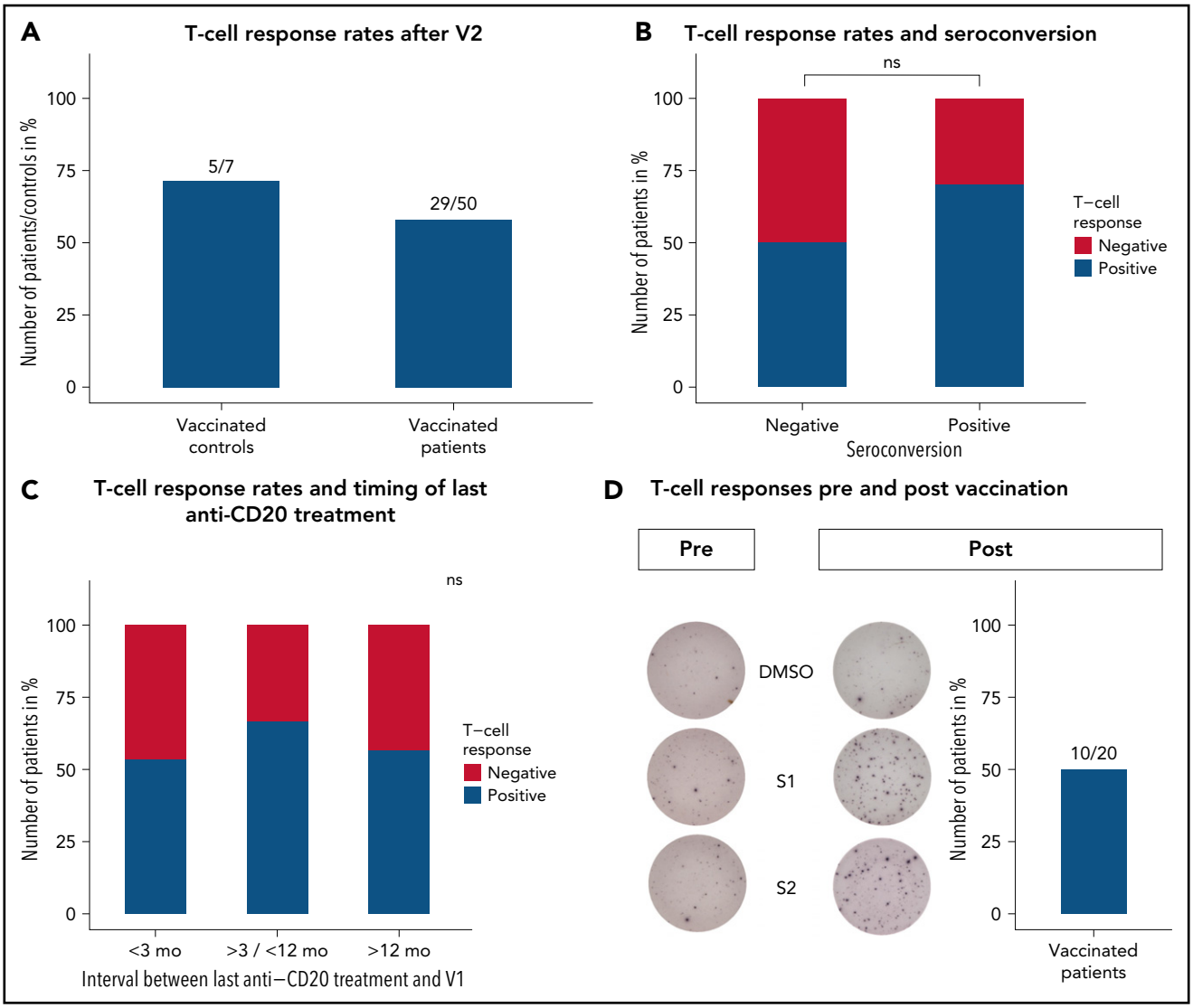


Figure 2. T-cell responses after COVID-19 vaccination in anti-CD20-treated lymphoma patients. (A) T-cell response rates in vaccinated patients (n = 50) and vaccinated healthy controls (n = 7) both after V2. A response was considered positive if mean spot-forming units (SFU) in peptide stimulated wells was >3 SFU above background, defined as mean SFU + 2 standard deviations of dimethylsulfoxide (DMSO)-exposed wells. Staphylococcal Enterotoxin B (SEB) served as the positive control. The median time between second vaccination and sample collection was 17 days (IQR 14–21 days) in the vaccinated patient cohort and 18 days (IQR 14–80 days) in the healthy control cohort. The T-cell response rate in the vaccinated healthy cohort was 71% (5/7) and 58% in the patient cohort with previous or ongoing anti-CD20 treatment (29/50). In patients and healthy controls with an available sample prior to vaccination, we observed positive T-cell responses (6 out of 26 patients, 1 out of 9 healthy controls, data not shown). These positive T-cell responses without prior COVID-19 infection were interpreted as a crossreactive response of memory T cells after prior infection with common cold coronaviruses. (B) T-cell response rates according to the anti-S1 seroconversion after the second vaccination. The T-cell response rate of patients with a successful seroconversion was 70% (14/20). Patients without a seroconversion still showed a T-cell response in 50% (15/30). The difference in T-cell response rates between patients with and without a seroconversion was not statistically significant (Fisher's exact test $P = .2$). (C) T-cell response rates after second vaccination according to the interval of last anti-CD20 treatment and first COVID-19 vaccination (<3 months: n = 15, >3 months and <12 months: post n = 12; >12 months: n = 23). The T-cell response rate was 57% (13/23), 67% (8/12), and 53% (8/15) when the last anti-CD20 treatment was administered >12 months, within >3 and <12 months, or <3 months prior to vaccination, respectively. No significant difference of the T-cell response between all 3 groups was observed (Fisher's exact test: >12 months vs >3 months and <12 months, $P = .7$; >12 months vs <3 months, $P = 1.0$; >3 months and <12 months vs <3 months, $P = .7$). (D) T-cell responses in patients with a proven negative prevaccination T-cell status. For 26 patients, prevaccination samples (median time of sample collection: 218.5 days [IQR 4.5–309 days]) prior to vaccination were available and tested for T-cell response. Out of the 26 patients, 20 patients had a negative T-cell response prior to vaccination. Representative ELISpot images were shown for a patient with diffuse large B-cell lymphoma who was treated with rituximab-CHOP and received the last cycle 48 days prior to the first vaccination. This patient had no SARS-CoV-2-S1 antibody response after 2 vaccinations with BNT162b2 (BioNTech). The left ELISpot panel shows the negative T-cell response measured in the sample 1 day prior to vaccination. The right ELISpot panel shows a positive T-cell response after 2 COVID-19 vaccinations (sample collection: 14 days post-second vaccination). The right bar plot shows the T-cell response rate after V2 in patients with a confirmed negative T-cell response prior to vaccination (n = 20). A positive T-cell response after vaccination was observed in 50% of patients (10/20). V1, vaccination 1; V2, vaccination 2; ns, not significant.

7 vaccinated healthy controls (71%) (Figure 2A). Seventy percent of seroconverted patients exhibited a T-cell response, whereas 50% of patients without a seroconversion still showed a T-cell response (Figure 2B). In contrast to serological responses, we did not find that vaccine-induced T-cell responses were dependent on the interval between the last anti-CD20 treatment and the vaccination (Figure 2C). The rate of T-cell responses was not reduced in patients receiving chemotherapy and anti-CD20

treatment compared with anti-CD20 monotherapy (Figure S3). SARS-Cov-2 specific T-cell responses in individuals without COVID-19 vaccination or a history of COVID-19 infection were previously reported and interpreted as a crossreactive response of memory T cells after prior infection with common cold coronaviruses.[14,15] We therefore analyzed T-cell responses in a subset of patients (n = 26) prior to COVID-19 vaccination (median time of sample collection: 218.5 days [IQR 4.5–309 days] prior to vaccination) and after vaccination. In patients with a proven negative prevaccination T-cell response (n = 20), we observed a seroconversion independent T-cell response comparable to the complete cohort (seroconversion vs no seroconversion: 56% vs 45%, $P = 1.0$) (Figure 2D; supplemental Figure S4). It is noteworthy that we and others[8,15] also observed that healthy controls can exhibit negative ELISpot results after COVID-19 vaccination despite successful seroconversion. If these ELISpot assays represent false-negative test results, we might underestimate the true percentages of patients developing T-cell immunity after COVID-19 vaccination.

Potential limitations of this study include the relatively small number of patients, the lack of a predefined sample collection, and the lack of large healthy reference cohorts. Thus, these initial data in anti-CD20-treated lymphoma patients need to be confirmed in larger prospective studies. However, our results suggest that patients with recent or ongoing anti-CD20 treatments who suffer from insufficient humoral immune responses after 2 COVID-19 vaccinations might still benefit from vaccination due to the cellular immune response. T-cell responses could be of particular importance for patients who get infected with COVID-19 because effective T-cell responses are essential for viral clearance.[16] Of note, even if infections cannot be prevented, it is still possible that T-cell responses are sufficient to ensure a mild course of COVID-19 disease. Taken together, COVID-19 vaccinations might be beneficial for anti-CD20-treated patients due to T-cell immunity.

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Authorship

Contribution: N.L. and S.D. initiated and designed the study; N.L., P.-M.B., I.K., J.M., and P.D. collected clinical data; C.S. and L.B. performed the measurement of neutralizing antibodies; P.S. performed the serologic antibody testing; I.P. performed and analyzed the cellular T-cell testing; N.L. and S.D. analyzed data and performed statistical analysis; N.L., S.D., C.S., and I.P. wrote the paper; and N.L., C.S., L.B., P.-M.B., I.K., J.M., P.S., H.-G.K., C.M.-T., P.D., and S.D. edited the manuscript.

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Footnotes

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