TO THE EDITOR:

Activity of mRNA COVID-19 vaccines in patients with lymphoid malignancies

Jennifer L. Crombie,1,2,* Amy C. Sherman,1,3,* Chi-An Cheng,2,4,5 Christine E. Ryan,1,2 Rebecca Zon,1,2 Michaël Desjardins,1,3,6 Peter Baker,1 Mikaela McDonough,1 Natalie Izaguirre,1,3 Bruce Bausk,3 Jonathan Krauss,3 Tal Gilboa,2,4,5 Yasmeen Senussi,4 David R. Walt,2,4,5 Matthew S. Davids,1,2 Jennifer R. Brown,1,2 Philippe Armand,1,2 Lindsay R. Baden,1,3 † Nicolas Issa,1-3 †

1Dana-Farber Cancer Institute, Boston, MA; 2Harvard Medical School, Boston, MA; 3Department of Medicine and 4Department of Pathology, Brigham and Women’s Hospital, Boston, MA; 5Wyss Institute for Biologically Inspired Engineering, Harvard University, Boston, MA; and 6Division of Infectious Diseases, Centre Hospitalier de l’Université de Montréal, Montreal, QC, Canada

Patients with lymphoid malignancies are at increased risk of developing COVID-19 and are at high risk of poor outcomes.1-5 There is a need for protective strategies in this vulnerable population. Although there have been 2 prior phase 3 trials investigating nanoparticle-encapsulated messenger RNA (mRNA)-based vaccines, BNT162b2 (Pfizer, Inc) and mRNA-1273 (ModernaTX, Inc), that encode the prefusion stabilized full-length spike (S) protein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), immunocompromised patients were excluded.6,7 In the research by Perry et al, humoral responses following administration of BNT162b2 were evaluated in patients with non-Hodgkin lymphoma. Strikingly, patients who had received anti-CD20 antibody therapy within 6 months of vaccination were unlikely to mount a humoral response, a finding that has similarly been described in patients with chronic lymphocytic leukemia (CLL).8,9 Perry et al also showed that patients with treatment-naive disease were more likely to develop a humoral response, although with lower rates and titer levels as compared with healthy controls. We similarly performed a prospective study to evaluate serologic response following vaccination with BNT162b2 or mRNA-1273 in a cohort of patients with key lymphoid malignancies (including CLL) in various phases of treatment. Our data support the findings by Perry et al. In addition, we report quantitative antibody titers at 3 time points pre- and postvaccination and describe the humoral response following a range of treatment strategies.

Patients were eligible for enrollment if they had a diagnosis of a lymphoid malignancy and were planning to receive either the BNT162b2 or mRNA-1273 vaccine. Patients who had received chimeric antigen receptor therapy (CAR-T) or autologous stem cell transplant were vaccinated at least 3 months after cellular therapy, and all other patients were vaccinated per patient and provider preference. Healthy volunteers were included as controls who were health care workers 18 years old at Brigham and Women’s Hospital and had no prior history of COVID-19 infection. This study was approved by the Dana-Farber/Harvard Cancer Center Institutional Review Board and the Brigham and Women’s Hospital Institutional Review Board, and all participants provided written informed consent. Blood was drawn at baseline prior to the first vaccine dose, at the time of the second vaccine dose, and ~28 days later. Using the multiplexed, single-molecule array assay, quantitative detection of immunoglobulin G (IgG) antibodies (in a unit of normalized average enzymes per bead) against the S protein and nucleocapsid (N) proteins was assessed in serological samples.10,11 Antibody values for healthy adults prepandemic (January to December 2019) sera were used to determine an internal threshold of positivity for anti-S IgG. The Mann-Whitney U test was used to compare the anti-S IgG magnitudes for the healthy cohort and lymphoid malignancy cohort. Statistical significance was considered at a level $\alpha = 0.05$ using GraphPad Prism software (Version 9.1.1; La Jolla, CA).

Twenty-three patients have completed the 2-dose vaccine series, and 21 of these patients have had follow-up at all 3 time points. Baseline characteristics are shown in Table 1. The median age at the time of vaccination was 69 years (range, 30-82 years). Sixteen (70%) patients received BNT162b2, and the remainder received mRNA-1273. Fourteen (61%) had CLL, and 9 (39%) had lymphoma, including 3 (13%) with diffuse large B-cell lymphoma (DLBCL), 3 (13%) with mantle cell lymphoma (MCL), and 1 (4%) each with
Follicular lymphoma, marginal zone lymphoma (MZL), and Hodgkin lymphoma (HL). Seventeen (74%) had received any prior anti-lymphoma treatment, with a median of 1 prior therapy (range, 1-3); 15 (65%) had received prior anti-CD20 antibody therapy, 6 (26%) within the past 12 months, including 3 patients with MCL on maintenance therapy; 3 patients had received prior CAR-T within 12 months; and 1 patient had received an autologous stem cell transplant within 6 months.

No patients had detectable anti-N IgG (Figure 1A) at baseline, implying no serologic evidence of prior natural infection with SARS-CoV-2. Baseline anti-S IgG titers were similar among patients in our cohort and healthy volunteers (n = 23) (P = .66) (Figure 1B). As compared with the healthy controls, the magnitude of anti-S IgG titers was significantly lower at the time of dose 2 (P = .0001) and ~28 days post-vaccine (P = .001) among patients with any lymphoid malignancy (Figure 1B).

We hypothesized that response could be differentiated by prior therapy. None of the patients (n = 6) who had received anti-CD20 antibody therapy within the past 12 months had an antibody response after the vaccine series (Figure 1C). Of note, 2 patients who received anti-CD19–directed CAR-T within 12 months developed anti-S IgG titers above our predetermined threshold; both of those patients had also received anti-CD20 antibody therapy >12 months from the time of vaccination. The other patient who had received CAR-T and anti-CD20 antibody therapy within the past 12 months did not develop anti-S IgG titers. One patient who had completed therapy with brentuximab vedotin, doxorubicin, vinblastine, and dacarbazine for HL 2 months prior developed IgG S antibodies. All patients who were treatment-naive, including 5 patients with CLL and 1 patient with MZL, developed anti-S IgG titers by day 28 post-vaccine series (Figure 1D). Interestingly, as compared with the healthy cohort, there was a significant difference at the time of dose 2, with the treatment-naive cohort having a lower magnitude of response (P = .017), suggesting that at least 2 doses are needed to achieve a humoral response. Among CLL patients on Bruton tyrosine kinase inhibitors (n = 6), 3 had a serologic response. There was 1 CLL patient on venetoclax, without prior CD20 antibody therapy within the last 12 months, who did not develop anti-S IgG antibodies.

One patient with DLBCL who was 3 months post-CAR-T developed COVID-19, with persistent fever requiring hospitalization, 1 week after the first dose of vaccination and subsequently withdrew from the study and was not included. The patient has since made a full recovery. No other patients in our cohort developed COVID-19 following vaccination.

Our data are limited by the small sample size and the heterogeneous nature of our cohort. Healthy controls were also generally younger than those patients with a lymphoid malignancy. The threshold titer that confers protection against the SARS-CoV-2 has also yet to be established, and clinical efficacy cannot be determined. Furthermore, the role of T-cell immunity in the protection against COVID-19 remains unknown. However, as it has been shown by Perry et al, our study demonstrates impairment in humoral response in select patients with lymphoid malignancies, most notably those who have received recent anti-CD20 antibody therapy. Our data and those presented by Perry et al have implications for the use and timing of vaccination (and potentially booster immunizations) in this patient population. Importantly, not only is the timing of vaccination from CD20 therapy important but also the underlying disease state as demonstrated by Figure 3B from Perry et al, suggesting that nuanced recommendations for patients by both disease state and therapies are needed. By following humoral responses after both the first and the second dose, we also demonstrate that 2 doses are necessary even for treatment-naive patients to achieve the same humoral response as compared with healthy controls. In sum, patients with lymphoid malignancies should not be assumed to be protected from vaccination and should remain maximally prudent to avoid infection. Conversely, our findings suggest that humoral response can be seen following cytotoxic chemotherapy, in patients receiving anti-CD19–directed cellular therapy, and among patients who have not received prior therapy, even with CLL.

In conclusion, our study provides further data to support that patients with lymphoid malignancies, and most dramatically those with recent anti-CD20 monoclonal antibody treatment, have reduced humoral responses to mRNA COVID-19 vaccines as compared with healthy controls. Larger studies are needed to further assess humoral response to vaccination within specific malignancy and treatment subgroups, clinical efficacy, and durability of protection in this population.
Acknowledgments
The authors thank Xiaofang Li, Salena Von, and John Kupelian, who assisted in the processing of samples, and Megan Powell, Julia Klopfer, and Noah Abasciano, who assisted with clinic coordination and phlebotomy for the participants.

Authorship
Contribution: J.L.C., A.C.S., L.R.B., and N. Issa designed research, performed research, analyzed data, and wrote the paper; and C.-A.C., C.E.R., R.Z., M.D., P.B., M.M., N. Izaguirre, B.B., J.K., T.G., Y.S., D.R.W., M.S.D., J.R.B., and P.A. performed research, analyzed the data, and provided critical review of the manuscript.

Conflict-of-interest disclosure: J.L.C. reports grant support, paid to her institution from Abbvie and Bayer, and consulting fees from Incyte and Karyopharm. A.C.S. reports research funding from Merck. R.Z. reports consulting fees and is a stockholder for Amagma Therapeutics. M.S.D. reports receiving grant support, paid to his institution, and consulting fees from Ascentage Pharma, AstraZeneca, BMS, Genentech,

Figure 1. COVID-19 antibody responses in patients with CLL/lymphoma and healthy controls. (A) The IgG N antibody responses at baseline, time of dose 2, and 28 days after vaccination for the healthy cohort (red) and CLL/lymphoma cohort (blue). Low magnitudes at all time points demonstrate no prior history of natural infection or infection with COVID-19 during the study. (B) IgG S antibody titers in healthy cohort (red) \( (n = 23) \), as compared with the CLL/lymphoma cohort (blue) \( (n = 23) \). (C) The magnitude of IgG S antibody for patients who received CD20 therapy in the last 12 months (blue) \( (n = 6) \), as compared with those who received CD20 beyond 12 months (red) \( (n = 9) \). (D) IgG S antibody responses for the healthy cohort (red) \( (n = 23) \), as compared with patients with CLL/lymphoma who were treatment-naive (blue) \( (n = 5) \). The dotted horizontal line in panels B–D at 1.07 is an internally validated threshold that marks a positive or negative antibody response. The black error bars denote median with a 95% confidence interval AEB, average enzymes per bead.
MEI Pharma, Novartis, TG Therapeutics, and Verastem, grant support, paid to his institution from Surface Oncology, and consulting fees from AbbVie, Adaptive Biotechnologies, BeiGene, Celgene, Eli Lilly, Janssen, Merck, Research to Practice, and Takeda. J.R.B. reports research funding, to her institution, from Gilead, Loxo, Sun, and Verastem; has been a consultant for AbbVie, Acerta, AstraZeneca, BeiGene, Catalent, Dynamo, Eli Lilly, Genentech/Roche, Gilead, Juno/Celgene, Kite, Loxo, MEI Pharma, Nextceoa, Novartis, Octapharma, Pﬁzer, Pharmacyclics, Redx, Sun, Sunesis, TG Therapeutics, and Verastem; has received honoraria from Janssen and Teva; and is on Data Safety Monitoring Committees for Morphosys and Inveictys. P.A. reports grant support, to his institution, from Merck, BMS, Afﬁmed, Adaptive, Roche, Tensha, Otsuka, Sigma Tau, Genentech, IGM, Kite, honoraria from Merck, BMS, and consulting fees from Merck, BMS, Pfizer, Afﬁmed, Adaptive, Infinity, ADC Therapeutics, Celgene, Morphosys, Daichi Sankyo, Miltenyi, Tessa, GenMab, C4, Enterome, Regeneron, Epizyme, AstraZeneca, Genentech. N. Issa receives research funds from Merck, GSK, Astellas and AiCuris. The remaining authors declare no competing financial interests.

ORCID proﬁles: J.L.C., 0000-0003-3445-5129; A.C.S., 0000-0002-6075-3990; C.-A.C., 0000-0002-6657-9137; M.D., 0000-0003-4028-4507; B.B., 0000-0003-4519-6898; T.G., 0000-0001-8172-7786; Y.S., 0000-0002-6881-5455; D.R.W., 0000-0002-5524-7348; J.R.B., 0000-0003-2040-4961.

Correspondence: Jennifer L. Crombie, Dana-Farber Cancer Institute, 450 Brookline Ave, Boston, MA 02215; e-mail: jennifer_crombie@dfci.harvard.edu.

References

1. Mato AR, Roeker LE, Lamanna N, et al. Outcomes of COVID-19 in patients with CLL: a multicenter international experience. Blood. 2020;136(10):1134-1143.

2. Sharma A, Bhatt NS, St Martin A, et al. Clinical characteristics and outcomes of COVID-19 in haematopoietic stem-cell transplantation recipients: an observational cohort study. Lancet Haematol. 2021;8(3):e185-e193.

3. Camargo JF, Mendoza MA, Lin R, et al. Clinical presentation and outcomes of COVID-19 following hematopoietic cell transplantation and cellular therapy [published online ahead of print 25 April 2021]. Transpl Infect Dis. doi:10.1111/tid.13625.

4. Duléry R, Lamure S, Delord M, et al. Prolonged in-hospital stay and higher mortality after Covid-19 among patients with non-Hodgkin lymphoma treated with B-cell depleting immunotherapy [published online ahead of print 28 April 2021]. Am J Hematol. doi:10.1002/ajh.26209.

5. Scarfo L, Chatzikonstantinou T, Rigolin GM, et al. COVID-19 severity and mortality in patients with chronic lymphocytic leukemia: a joint study by ERIC, the European Research Initiative on CLL, and CLL campus. Leukemia. 2020;34(9):2354-2363.

6. Polack FP, Thomas SJ, Kitchin N, et al; C4591001 Clinical Trial Group. Safety and efﬁcacy of the BNT162b2 mRNA Covid-19 vac- cine. N Engl J Med. 2020;383(27):2603-2615.

7. Baden LR, El Sahly HM, Essink B, et al; COVE Study Group. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med. 2021;384(5):403-416.

8. Herishanu Y, Avivi I, Aharon A, et al. Efficacy of the BNT162b2 mRNA COVID-19 vaccine in patients with chronic lymphocytic leukemia. Blood. 2021;137(23):3165-3173.

9. Roeker LE, Knorr DA, Thompson MC, et al. COVID-19 vaccine efﬁcacy in patients with chronic lymphocytic leukemia [published online ahead of print 13 May 2021]. Leukemia. doi:10.1038/s41375-021-01270-w.

10. Norman M, Gilboa T, Ogata AF, et al. Ultrasensitive high-resolution proﬁling of early seroconversion in patients with COVID-19. Nat Biomed Eng. 2020;4(12):1180-1187.

11. Ogata AF, Cheng CA, Desjardins M, et al. Circulating SARS-CoV-2 vaccine antigen detected in the plasma of mRNA-1273 vaccine recipients [published online ahead of print 20 May 2021]. Clin Infect Dis. doi:10.1093/cid/cia465.