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ORIGINAL ARTICLE

Safety and immunogenicity of a third dose of mRNA-1273 vaccine among cancer patients

Anna Giuliano[1] | **Barbara Kuter**[2] | **Shari Pilon-Thomas**[3] | **Junmin Whiting**[4] | **Qianxing Mo**[4] | **Brett Leav**[2] | **Bradley Sirak**[1] | **Christopher Cubitt**[5] | **Christopher Dukes**[3] | **Kimberly Isaacs-Soriano**[6] | **Kayoko Kennedy**[6] | **Somedeb Ball**[7] | **Ning Dong**[7] | **Akriti Jain**[7] | **Patrick Hwu**[3] | **Jeffrey Lancet**[7]

[1]Department of Cancer Epidemiology, Moffitt Cancer Center, Tampa, Florida, USA

[2]Moderna, Cambridge, Massachusetts, USA

[3]Department of Immunology, Moffitt Cancer Center, Tampa, Florida, USA

[4]Department of Biostatistics and Bioinformatics, Moffitt Cancer Center, Tampa, Florida, USA

[5]Immune Monitoring Core, Moffitt Cancer Center, Tampa, Florida, USA

[6]Non-Therapeutic Research Office (NTRO), Moffitt Cancer Center, Tampa, Florida, USA

[7]Department of Malignant Hematology, Moffitt Cancer Center, Tampa, Florida, USA

Correspondence
Jeffrey E Lancet, MD, Chair, Department of Malignant Hematology; Moffitt Cancer Center, Tampa, 33612, Florida, United States of America.
Email: jeffrey.lancet@moffitt.org

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Abstract

Background: Compared to the general population, cancer patients are at higher risk of morbidity and mortality following SARS-CoV-2 infection. The immune response to a two-dose regimen of mRNA vaccines in cancer patients is generally lower than in immunocompetent individuals. Booster doses may meaningfully augment immune response in this population. We conducted an observational study with the primary objective of determining the immunogenicity of vaccine dose three (100 μg) of mRNA-1273 among cancer patients and a secondary objective of evaluating safety at 14 and 28 days.

Methods: The mRNA-1273 vaccine was administered ~7 to 9 months after administering two vaccine doses (i.e., the primary series). Immune responses (enzyme-linked immunosorbent assay [ELISA]) were assessed 28 days post-dose three. Adverse events were collected at days 14 (± 5) and 28 (+5) post-dose three. Fisher exact or X^2 tests were used to compare SARS-CoV-2 antibody positivity

Abbreviations: ACIP, Advisory Committee on Immunization Practices; BTK, Bruton's tyrosine kinase; CAR-T, chimeric antigen receptor T-cell; COVID-19, coronavirus disease 2019; ELISA, enzyme-linked immunosorbent assay; GMTs, geometric mean titers; HM, hematologic malignancies; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; IRB, Institutional Review Board; MCC, Moffitt Cancer Center; STROBE, STrengthening the Reporting of OBservational Studies in Epidemiology..

rates, and paired *t*-tests were used to compare SARS-CoV-2 antibody geometric mean titers (GMTs) across different time intervals.

Results: Among 284 adults diagnosed with solid tumors or hematologic malignancies, dose three of mRNA-1273 increased the percentage of patients seropositive for SARS-CoV-2 antibody from 81.7% pre-dose three to 94.4% 28 days post-dose three. GMTs increased 19.0-fold (15.8-22.8). Patients with lymphoid cancers or solid tumors had the lowest and highest antibody titers post–dose three, respectively. Antibody responses after dose three were reduced among those who received anti-CD20 antibody treatment, had lower total lymphocyte counts and received anticancer therapy within 3 months. Among patients seronegative for SARS-CoV-2 antibody pre-dose three, 69.2% seroconverted after dose three. A majority (70.4%) experienced mostly mild, transient adverse reactions within 14 days of dose three, whereas severe treatment-emergent events within 28 days were very rare (<2%).

Conclusion: Dose three of the mRNA-1273 vaccine was well-tolerated and augmented SARS-CoV-2 seropositivity in cancer patients, especially those who did not seroconvert post–dose two or whose GMTs significantly waned post–dose two. Lymphoid cancer patients experienced lower humoral responses to dose three of the mRNA-1273 vaccine, suggesting that timely access to boosters is important for this population.

KEYWORDS

Cancer, Coronavirus disease 2019, Immunogenicity, Observational study, Vaccination

1 | INTRODUCTION

Patients diagnosed with cancer are at higher risk of morbidity and mortality following SARS-CoV-2 infection than the general population [1]. We and others have previously demonstrated that immune responses following two doses of a COVID-19 vaccine induce highly variable SARS-CoV-2 antibody seroconversion rates, with lower geometric mean titers (GMTs) in this population than in healthy adults [2–9]. Generally, there is strong evidence supporting the waning clinical efficacy of an initial series of COVID-19 vaccination at approximately 6 months, an observation that may relate to reduced duration of humoral response, particularly in older adults [10, 11]. Within the cancer patient population specifically, loss of or reduction in humoral response following the initial series of COVID-19 vaccination may be even more pronounced [12]. These data suggest that patients diagnosed with cancer could benefit from dose three of the COVID-19 vaccine.

We previously conducted an observational study to evaluate the safety and immunogenicity of a two-dose regimen of 100 μg of mRNA-1273 vaccine (Moderna) in cancer patients diagnosed with solid tumors and hematologic malignancies (HM) [2]. In a follow-up to this, we conducted a second observational study with the primary objective of determining the immunogenicity of dose three of the mRNA-1273 vaccine in cancer patients. Herein, we report on both immunogenicity and safety results through day 28 after dose three. In this report, we also describe a sub-cohort of cancer patients who participated in both observational studies, allowing for an immune response assessment after each of the three vaccine doses.

2 | METHODS

2.1 | Subject eligibility and consent

All cancer patients enrolled in this observational study ($n = 284$) had a documented history of previously receiving two doses of mRNA-1273 approximately one month apart between January and March of 2021 at Moffitt Cancer Center (MCC; Tampa, Florida, United States of America). A subset of patients ($n = 130$) also had participated in an earlier study of a two-dose regimen, in which seroconversion (to SARS-CoV-2 antibody positivity) and SARS-CoV-2 GMTs pre-vaccination and post-vaccine doses one and

two were available for analysis, henceforth referred to as Cohort 1 [2]. Other analyzed cohorts included the subset of patients who were SARS-CoV-2 antibody-negative prior to dose 3 and the subset of patients who remained antibody-negative following dose 3. Key eligibility criteria included: (1) 18 years of age or older; (2) documented cancer history; (3) completed two mRNA-1273 vaccine series prior to March 31, 2021; and (4) had no known or suspected allergy or history of anaphylaxis, urticaria, or other significant adverse reaction to the vaccine or its excipients. The study was approved by the Advarra Institutional Review Board (IRB) per protocol Pro00056961. All patients provided written informed consent. This study followed the STrengthening the Reporting of OBservational Studies in Epidemiology (STROBE) reporting guidelines.

2.2 | Study procedures and data collection

A third 100 μg dose of mRNA-1273 was administered intramuscularly to each patient between October and December 2021. Dose three administration was consistent with emergency use authorization published by the United States Federal Drug Administration on August 12, 2021, for a third 100 μg dose to be administered at least 28 days following the two-dose regimen, which was issued two months prior to the start of the study enrolment. For the purposes of determining the primary study objective (immunogenicity), serum samples were collected immediately prior to administration of dose three and on day 28 post–dose three (+ 14 days). For the secondary objective, safety data were collected 14 days (±5) and 28 days (+14 days) post-vaccination using a standardized questionnaire administered by staff interview of vaccine recipients (Supplementary Materials). Data collected included local and systemic reactions and serious adverse events. In addition, an electronic health record review was conducted for all patients to validate patient-reported adverse events and to determine any laboratory-defined adverse events within this timeframe (28 days + 14 days after vaccine dose three).

2.3 | Assay for SARS-COV-2 antibody detection and quantification

The enzyme-linked immunosorbent assay (ELISA) used to assess immunogenicity has been previously described [2]. The human SARS-COV-2 serology standard provided by the Frederick National Laboratory (National Institute of Health) was used to quantify GMTs. The assay's limit of detection (above which was defined as a positive result) was calculated as the mean optical density of pooled negative control sera plus 3 standard deviations. The mean concentration at the limit of detection was 25 AU/mL.

2.4 | Statistical analysis

Descriptive statistics (proportions and frequencies for categorical variables and medians [ranges] for continuous variables) were used to summarize patient characteristics. The primary study objective was to assess immunogenicity following dose three of the mRNA-1273 vaccine. To enable a quantitative estimate of an immune response, antibody-negative patients were assigned an imputed value of 12.5, which was halfway between 0 and the assay's detection limit (25 AU/mL). Binding antibody IgG geometric mean titers (GMTs) and their 95% confidence intervals were calculated based on $\log_{10}$-transformed titers and t-distribution, then transformed back to the original scale. The 95% confidence intervals of fold change were calculated based on the t-distribution of the difference in the $\log_{10}$-transformed titers, then transformed back to the original scale. Fisher exact or x^2 tests were used to compare SARS-CoV-2 antibody positivity rates across patient characteristics; the Fisher exact test was used when any of the cell counts were <5. The Kruskal-Wallis test was used to evaluate the association between SARS-CoV-2 GMTs and patient characteristics. Paired *t*-tests were used to compare SARS-CoV-2 GMTs ~7 to 9 months after dose two to levels 29 days after dose three. Observations with missing data were removed from the analyses. All analyses were performed using SAS, version 9.4 (SAS Institute, Inc) and R software, version 4.0.2 (R Foundation for Statistical Computing). Two-sided $P < 0.05$ was considered statistically significant.

3 | RESULTS

3.1 | Patient characteristics

Baseline characteristics of the entire population and Cohort 1 are depicted in Table 1. A total of 284 patients diagnosed with cancer were included in the study, among whom 157 (55.3%) were diagnosed with HM and 127 (44.7%) with solid tumor malignancies. All received dose three of mRNA-1273 between August 24, 2021, and December 17, 2021, ~7 to 9 (median of 7.4) months after the second dose. The median age of participants at the time of dose three was 67 years, and 46.5% were female; 90.8% of patients were White, 5.3% were Black, and 7.0% were Hispanic. Only 2 of the overall study participants ($n = 284$) reported SARS-CoV-2 infection prior to receipt of dose 3 of mRNA-1273.

TABLE 1 Study population demographics of all cancer study patients and cohort 1 sub-population.

Characteristics	All cancer patients ($n = 284$) *n* (%)	Cohort 1 sub-population[¶] ($n = 130$) *n* (%)
Time interval (months) from the second dose to dose three (median, range)	7.4 (6.8-9.0)	7.4 (6.9-9.0)
Age group (median age 67 years)		
≤67 years	145 (51.1)	73 (56.2)
>67 years	139 (48.9)	57 (43.8)
Gender		
Male	152 (53.5)	68 (52.3)
Female	132 (46.5)	62 (47.7)
Ethnicity		
Hispanic	20 (7.0)	5 (3.8)
Non-Hispanic	264 (93.0)	125 (96.2)
Race		
White	258 (90.8)	124 (95.4)
Black	15 (5.3)	4 (3.1)
Asian	3 (1.1)	1 (0.8)
Other	8 (2.8)	1 (0.8)
Primary patient category		
Hematological malignancies	157 (55.3)	82 (63.1)
Myeloid disorders	38 (24.2)	19 (23.2)
Lymphoid disorders	67 (42.7)	35 (42.7)
Plasma cell disorders	52 (33.1)	28 (34.1)
Solid tumors	127 (44.7)	48 (36.9)
Disease status		
Previously untreated	23 (8.1)	7 (5.4)
Remission	171 (60.2)	95 (73.1)
Relapse/refractory/stable disease	90 (31.7)	28 (21.5)
Lymphocyte count[a]		
$>1 \times 10^9$/L	152 (65.0)	67 (67.0)
$\leq 1 \times 10^9$/L	82 (35.0)	33 (33.0)
Among Plasma Cell Disorders		
IgG level[a]		
<700 mg/dL	28 (56.0)	16 (59.3)
≥700 mg/dL	22 (44.0)	11 (40.7)
IgA level[a]		
<70 mg/dL	26 (52.0)	14 (51.9)
≥70 mg/dL	24 (48.0)	13 (48.1)
IgM level[a]		
<40 mg/dL	40 (80.0)	20 (74.1)
≥40 mg/dL	10 (20.0)	7 (25.9)
Received anticancer therapy within 3 months[b]		
No	160 (56.3)	75 (57.7)
Yes	124 (43.7)	55 (42.3)
Small molecules[c]		
No	227 (79.9)	98 (75.4)
Yes	57 (20.1)	32 (24.6)

(Continues)

TABLE 1 (Continued)

Characteristics	All cancer patients ($n = 284$) n (%)	Cohort 1 sub-population[¶] ($n = 130$) n (%)
Anti-CD20 antibodies within 6 months		
No	273 (96.1)	124 (95.4)
Yes	11 (3.9)	6 (4.6)
Anti-CD38 antibodies within 6 months		
No	270 (95.1)	120 (92.3)
Yes	14 (4.9)	10 (7.7)
Patients treated with cellular therapy		
No	243 (85.6)	104 (80.0)
Yes	41 (14.4)	26 (20.0)
Patients treated with cellular therapy type		
Allo-HSCT any time prior to vaccination	22 (53.7)	14 (53.8)
Auto-HSCT within the past 24 months	13 (31.7)	8 (30.8)
CD19 CAR-T any time prior to vaccination	5 (12.2)	3 (11.5)
BCMA CAR-T any time prior to vaccination	1 (2.4)	1 (3.8)
BTK inhibitors		
No	278 (97.9)	129 (99.2)
Yes	6 (2.1)	1 (0.8)
Line of systemic therapy to date		
0	67 (23.6)	23 (17.7)
1	115 (40.5)	54 (41.5)
≥2	102 (35.9)	53 (40.8)
SARS-CoV-2 infection prior to vaccine dose 1		
Yes	1 (0.4)	1 (0.8)
No/unknown	283 (99.6)	129 (99.2)

[a]All lab assessments were within 3 months before dose three of the vaccine, and 17.6% of total patients had missing lymphocyte count data. Among patients with plasma cell disorders, 3.8% had missing IgG values, 3.8% had missing IgA values, and 3.8% had missing IgM values.
[b]Anti-androgen and anti-estrogen hormonal therapies were not considered anticancer therapy for this study.
[c]Small molecules include tyrosine kinase inhibitors, proteasome inhibitors, lenalidomide, pomalidomide, and venetoclax.
[¶]The 3-dose cohort includes the subset of patients who had safety and immunogenicity data after doses 1, 2, and 3.

In total, 60.2% of all HM and solid tumor patients were in remission, and 65.0% had a lymphocyte count $>1 \times 10^9$/mL at the time of receipt of dose three of the vaccine (Table 1). Among the 157 patients diagnosed with HM, 24.2% had myeloid disorders, 42.7% had lymphoid disorders, and 33.1% had plasma cell disorders/malignancies.

3.2 | Adverse events

Dose three of mRNA-1273 was generally well tolerated (Table 2). The most common adverse event reported within 14 days (± 5 days) and 28 days (+14 days) of dose three was mild injection site pain (reported by 51.1% and 5.6% of patients 14- and 28-days post–dose three, respectively). The next most common adverse events 14 days post–dose three included mild tiredness (18.0%), injection site redness/hardness (12.7%), and mild headache (12.3%). There were only 4 patients (1.4%) with protocol-defined severe adverse events, none of which were deemed related to the vaccine. No treatment-emergent laboratory adverse events were observed.

3.3 | Serum antibody concentrations increase after vaccine dose three

Overall, 81.7% of patients diagnosed with cancer were SARS-CoV-2 antibody seropositive ~7 to 9 (median of 7.4) months after vaccine dose two, with seropositivity ranging from 64.2% for lymphoid cancer patients to 89.8% for solid tumor cancer patients (Table 3). Twenty-eight days post–dose three, 94.4% of all study patients were seropositive, with percentages ranging from 82.1% for lymphoid

TABLE 2 Solicited local and systemic adverse events (AE) within 14 days and 28 days of receipt of dose 3 ($n = 284$).

Characteristics	No. patients (%)	
	Day 14 (+5 days)	Day 28 (+14 days)
Any symptoms	200 (70.4)	38 (13.4)
Fever	44 (15.5)	7 (2.5)
Injection site pain		
Mild	145 (51.1)	16 (5.6)
Mild-Moderate	26 (9.2)	3 (1.1)
Moderate	4 (1.4)	0 (0)
Severe	0 (0)	0 (0)
Arm swelling		
Mild	22 (7.7)	2 (0.7)
Mild-Moderate	10 (3.5)	1 (0.4)
Moderate	0 (0)	0 (0)
Severe	0 (0)	0 (0)
Injection site redness/hardness		
Mild	36 (12.7)	4 (1.4)
Mild-Moderate	7 (2.5)	1 (0.4)
Moderate	1 (0.4)	0 (0)
Severe	0 (0)	0 (0)
Chills		
Mild	26 (9.2)	3 (1.1)
Mild-Moderate	10 (3.5)	0 (0)
Moderate	11 (3.9)	1 (0.4)
Severe	0 (0)	0 (0)
Tiredness		
Mild	51 (18.0)	6 (2.1)
Mild-Moderate	37 (13.0)	5 (1.8)
Moderate	17 (6.0)	3 (1.1)
Severe	0 (0)	0 (0)
Headache		
Mild	35 (12.3)	3 (1.1)
Mild-Moderate	7 (2.5)	4 (1.4)
Moderate	8 (2.8)	1 (0.4)
Severe	0 (0)	0 (0)
Chest pressure/discomfort		
Mild	0 (0)	0 (0)
Mild-Moderate	1 (0.4)	0 (0)
Moderate	0 (0)	0 (0)
Severe	0 (0)	0 (0)
Dyspnoea/shortness of breath		
Mild	4 (1.4)	0 (0)
Mild-Moderate	0 (0)	0 (0)
Moderate	0 (0)	0 (0)
Severe	0 (0)	0 (0)

(Continues)

TABLE 2 (Continued)

Characteristics	No. patients (%) Day 14 (+5 days)	Day 28 (+14 days)
Palpitations (fast/irregular heartbeat)		
Mild	5 (1.8)	0 (0)
Mild-Moderate	1 (0.4)	0 (0)
Moderate	0 (0)	0 (0)
Severe	0 (0)	0 (0)
Joint pain/aches		
Mild	13 (4.6)	0 (0)
Mild-Moderate	9 (3.2)	3 (1.1)
Moderate	6 (2.1)	1 (0.4)
Severe	0 (0)	0 (0)
Nausea		
Mild	12 (4.2)	0 (0)
Mild-Moderate	3 (1.1)	0 (0)
Moderate	2 (0.7)	0 (0)
Severe	0 (0)	0 (0)
Swelling of lymph node under injection arm		
Mild	4 (1.4)	0 (0)
Mild-Moderate	3 (1.1)	1 (0.4)
Moderate	1 (0.4)	0 (0)
Severe	0 (0)	0 (0)
Muscle pain/aches		
Mild	15 (5.3)	2 (0.7)
Mild-Moderate	11 (3.9)	2 (0.7)
Moderate	9 (3.2)	1 (0.4)
Severe	0 (0)	0 (0)
Other	32 (11.3)	5 (1.8)

Participant-reported severity was assessed as: Mild: aware of but easily tolerated; Mild-Moderate: discomfort enough to cause interference with usual activities; Moderate: incapacitating, unable to work or do activities; Severe: requires emergency room visit or hospitalization.

cancer patients to 99.2% for solid tumor cancer patients. Overall, the GMT increased from 330.0 AU/mL pre–dose three to 6263.2 AU/mL post–dose three, a 19-fold (range, 15.8-22.8) titer increase. No differences in response to vaccine dose three were observed by age or gender (Table 3). As shown in Figure 1, pre–dose three and post–dose three antibody titers were highly variable among patients diagnosed with solid tumors as well as those with HM. Regardless of initial titer prior to dose three, all patient groups demonstrated a ≥10-fold increase in titer post–dose three (ranging from 10.5-fold for lymphoid patients to 25.5-fold for solid tumor patients). No difference in GMTs was observed based on the patient's disease status (previously untreated, in remission, or relapsed, refractory, or stable disease).

GMTs post–dose three were significantly lower ($P \leq 0.002$) among patients who had received anticancer therapy within three months as well as those treated with small molecules, anti-CD20 antibodies, or anti-CD38 antibodies within six months, and BTK inhibitors (Table 3). While no significant difference in response to vaccine dose three was noted between those who received cellular therapy and those who did not, it was notable that the 5 patients who had received CD19 CAR-T any time prior to dose three had very low GMTs pre– and post-dose three and showed only a 1.4-fold increase in titer post–dose three. Among the 52 patients with plasma cell disorders, GMTs were positively correlated to IgG, IgM, and IgA levels.

3.4 | Serum antibody responses in selected cohorts

Among the cohort of 130 patients from the original primary vaccine trial who had sera data pre–dose one, post–dose one, post–dose two, pre–dose three, and post–dose three,

TABLE 3 Percent SARS-CoV-2 antibody seropositive and geometric mean titer pre-vaccination and following receipt of vaccine dose three by cancer patient category and cancer treatment ($n = 284$).

Characteristics	*n*	% of SARS-CoV-2 antibody seropositive patients (95% CI)			GMTs, AU/mL (95% CI)			
		Pre-Dose 3	Post-Dose 3	*P* value*	Pre-Dose 3	Post-Dose 3	*P* value**	Fold increase
Overall	284	81.7 (76.7-86.0)	94.4 (91.0-96.8)		330.0 (265.3-410.5)	6,263.2 (5,003.4-7,840.2)		19.0 (15.8-22.8)
Age group (median age 66 years)				0.264			0.790	
≤67	145	86.2 (79.5-91.4)	95.9 (91.2-98.5)		442.7 (332.8-588.8)	6,536.7 (4,832.4-8,842.2)		14.8 (11.7-18.6)
>67	139	77.0 (69.1-83.7)	92.8 (87.2-96.5)		242.9 (175.0-337.1)	5,990.0 (4,275.4-8,392.2)		24.7 (18.7-32.6)
Gender				0.420			0.621	
Male	152	80.9 (73.8-86.8)	95.4 (90.7-98.1)		288.6 (214.1-389.0)	6,884.6 (5,161.6-9,182.8)		23.9 (18.4-30.9)
Female	132	82.6 (75.0-88.6)	93.2 (87.5-96.8)		385.1 (279.1-531.3)	5,616.7 (3,940.1-8,006.8)		14.6 (11.3-18.8)
Ethnicity				0.313			0.861	
Hispanic	20	75.0 (50.9-91.3)	90.0 (68.3-98.8)		270.5 (109.0-671.4)	4,507.2 (1,502.5-1,3520.5)		16.7 (7.4-37.5)
Non-Hispanic	264	82.2 (77.0-86.6)	94.7 (91.3-97.1)		335.0 (267.2-420.0)	6,421.2 (5,107.0-8,073.7)		19.2 (15.9-23.1)
Race				0.794			0.071	
White	258	80.2 (74.8-84.9)	94.2 (90.6-96.7)		308.9 (244.5-390.3)	5,968.6 (4,704.5-7,572.4)		19.3 (15.9-23.5)
Black	15	93.3 (68.1-99.8)	93.3 (68.1-99.8)		504.8 (225.2-1,131.6)	6,296.3 (2,120.4-18,696.2)		12.5 (6.3-24.6)
Asian	3	100.0 (29.2-100.0)	100.0 (29.2-100.0)		1,430.7 (433.7-4,719.6)	26,357.2 (3,548.1-195,793.7)		18.4 (7.7-44.1)
Other	8	100.0 (63.1-100.0)	100.0 (63.1-100.0)		722.6 (300.1-1,740.0)	17,107.3 (7,236.6-40,441.2)		23.7 (12.3-45.7)
Primary patient category[¶]				**0.001**			**<0.001**	
Hematological malignancies[#]	157	75.2 (67.6-81.7)	90.4 (84.7-94.6)	**0.011**	257.9 (186.2-357.4)	3,851.6 (2,669.9-5,556.4)	**0.048**	14.9 (11.5-19.4)
Myeloid disorders	38	86.8 (71.9-95.6)	97.4 (86.2-99.9)		378.5 (213.0-672.8)	8,682.5 (5,022.8-15,008.8)		22.9 (13.4-39.4)
Lymphoid disorders	67	64.2 (51.5-75.5)	82.1 (70.8-90.4)		204.4 (115.0-363.2)	2,150.2 (1,066.7-4,334.4)		10.5 (7.0-15.9)
Plasma cell disorders	52	80.8 (67.5-90.4)	96.2 (86.8-99.5)		263.0 (156.4-442.4)	4,506.7 (2,813.4-7,219.2)		17.1 (11.0-26.7)
Solid tumors	127	89.8 (83.1-94.4)	99.2 (95.7-100.0)		447.5 (341.4-586.6)	11,424.2 (9,623.4-13,562.0)		25.5 (20.1-32.5)
Disease status				0.617			0.790	
Previously untreated	23	82.6 (61.2-95.0)	100.0 (85.2-100.0)		351.0 (145.6-846.2)	7,630.6 (4,575.1-12,726.6)		21.7 (12.0-39.3)
Remission	171	84.2 (77.9-89.3)	94.2 (89.5-97.2)		393.0 (300.3-514.2)	6,578.6 (4,946.4-8,749.3)		16.7 (13.5-20.8)
Relapse/refractory/ stable disease	90	76.7 (66.6-84.9)	93.3 (86.1-97.5)		233.1 (154.7-351.2)	5,424.2 (3,468.6-8,482.5)		23.3 (15.9-34.0)
Lymphocyte count[a]				**0.002**			**<0.001**	
$>1 \times 10^9$/L	152	85.5 (78.9-90.7)	97.4 (93.4-99.3)		401.1 (301.6-533.6)	8,950.2 (7,009.2-11,428.7)		22.3 (17.5-28.4)
$\leq 1 \times 10^9$/L	82	67.1 (55.8-77.1)	85.4 (75.8-92.2)		179.8 (111.8-289.1)	2,248.5 (1,272.2-3,974.1)		12.5 (8.5-18.4)

(Continues)

TABLE 3 (Continued)

Characteristics	*n*	% of SARS-CoV-2 antibody seropositive patients (95% CI)			GMTs, AU/mL (95% CI)			
		Pre-Dose 3	Post-Dose 3	*P* value*	Pre-Dose 3	Post-Dose 3	*P* value**	Fold increase
Among plasma cell disorders								
IgG level[a]				0.497			**0.004**	
<700 mg/dL	28	78.6 (59.0-91.7)	92.9 (76.5-99.1)		201.6 (100.4-404.8)	2,447.6 (1,186.5-5,049.1)		12.1 (7.1-20.8)
≥700 mg/dL	22	81.8 (59.7-94.8)	100 (84.6-100.0)		333.7 (137.4-810.3)	9,185.8 (5,442.2-15,504.8)		27.5 (12.4-61.4)
IgA level[a]				0.491			**0.001**	
<70 mg/dL	26	73.1 (52.2-88.4)	92.3 (74.9-99.1)		164.1 (72.2-373.4)	2,098.1 (956.4-4,602.9)		12.8 (6.4-25.7)
≥70 mg/dL	24	87.5 (67.6-97.3)	100 (85.8-100.0)		399.8 (200.9-795.6)	9,721.6 (6,490.7-14,560.8)		24.3 (13.1-45.1)
IgM level[a]				0.363			**0.048**	
<40 mg/dL	40	80.0 (64.4-90.9)	97.5 (86.8-99.9)		219.9 (122.7-394.2)	3,914.6 (2,399.9-6,385.5)		17.8 (10.5-30.3)
≥40 mg/dL	10	80.0 (44.4-97.5)	90.0 (55.5-99.7)		431.4 (93.8-1,984.0)	6,864.0 (1,246.9-37,784.3)		15.9 (5.3-48.2)
Received anticancer therapy within 3 months [b]				**0.017**			**<0.001**	
No	160	90.6 (85.0-94.7)	97.5 (93.7-99.3)		509.2 (394.6-657.1)	9,448.7 (7,566.2-11,799.5)		18.6 (15.0-23.0)
Yes	124	70.2 (61.3-78.0)	90.3 (83.7-94.9)		188.6 (132.0-269.3)	3,684.5 (2,439.2-5,565.5)		19.5 (14.2-26.9)
Small molecules [c]				0.747			**<0.001**	
No	227	84.6 (79.2-89.0)	93.8 (89.9-96.6)		393.9 (310.8-499.1)	7,242.1 (5,633.0-9,310.8)		18.4 (15.1-22.4)
Yes	57	70.2 (56.6-81.6)	96.5 (87.9-99.6)		163.1 (97.4-273.1)	3,512.5 (2,159.7-5,712.8)		21.5 (13.7-34.0)
Anti-CD20 antibodies				**<0.001**			**<0.001**	
No	273	83.5 (78.6-87.7)	96.0 (92.9-98.0)		353.3 (284.6-438.5)	7,221.3 (5,879.7-8,869)		20.4 (17.1-24.5)
Yes	11	36.4 (10.9-69.2)	54.5 (23.4-83.3)		60.7 (11.7-314.8)	183.0 (23.3-1,436.8)		3.0 (1.0-9.4)
Anti-CD38 antibodies				1.000			**0.002**	
No	270	82.2 (77.1-86.6)	94.1 (90.6-96.6)		345.6 (277.1-431.1)	6,434.2 (5,086.5-8,139.0)		18.6 (15.5-22.4)
Yes	14	71.4 (41.9-91.6)	100 (76.8-100.0)		135.1 (38.4-475.7)	3,725.3 (2,435.6-5,697.8)		27.6 (10.1-75.6)
Patients treated with cellular therapy				0.262			0.461	
No	243	82.3 (76.9-86.9)	95.1 (91.5-97.4)		325.1 (258.2-409.4)	6,722.5 (5,342.4-8,459.2)		20.7 (17.1-25.1)
Yes	41	78.0 (62.4-89.4)	90.2 (76.9-97.3)		360.4 (183.4-708.0)	4,117.3 (1,908.0-8,884.5)		11.4 (6.6-19.7)

(Continues)

TABLE 3 (Continued)

Characteristics	*n*	% of SARS-CoV-2 antibody seropositive patients (95% CI)			GMTs, AU/mL (95% CI)			
		Pre-Dose 3	Post-Dose 3	*P* value*	Pre-Dose 3	Post-Dose 3	*P* value**	Fold increase
Patients treated with cellular therapy type								
Allo-HSCT any time prior to vaccination	22	81.8 (59.7-94.8)	95.5 (77.2-99.9)		433.3 (177.7-1,056.3)	6,429.1 (2,493.0-16,579.5)		14.8 (6.8-32.6)
Auto-HSCT within the past 24 months	13	92.3 (64.0-99.8)	100.0 (75.3-100.0)		522.5 (186.0-1,467.9)	8,438.8 (4,217.8-16,884.0)		16.2 (7.0-37.1)
CD19 CAR-T any time prior to vaccination	5	20.0 (0.5-71.6)	40.0 (5.3-85.3)		53.2 (1.0-2,964.9)	75.4 (2.0-2,817.2)		1.4 (0.4-5.6)
BCMA CAR-T any time prior to vaccination	1	100.0 (2.5-100.0)	100.0 (2.5-100.0)		712[d]	9,794.2[d]		13.8
BTK inhibitors				1.000			**0.002**	
No	278	82.4 (77.4-86.7)	94.2 (90.8-96.7)		340.6 (273.5-424.0)	6,504.3 (5,185.9-8,157.8)		19.1 (15.9-23.0)
Yes	6	50.0 (11.8-88.2)	100.0 (54.1-100.0)		76.7 (9.4-625.2)	1,088.2 (293.2-4,039.1)		14.2 (3.1-64.0)
Line of systemic therapy to date				0.847			0.929	
0	67	85.1 (74.3-92.6)	95.5 (87.5-99.1)		384.6 (246.7-599.4)	7,608.9 (5,083.5-11,388.9)		19.8 (13.8-28.4)
1	115	86.1 (78.4-91.8)	94.8 (89.0-98.1)		396.2 (289.0-543.1)	6,670.8 (4,783.2-9,303.4)		16.8 (13.1-21.6)
≥2	102	74.5 (64.9-82.6)	93.1 (86.4-97.2)		242.9 (162.6-362.9)	5,133.3 (3,331.8-7,908.7)		21.1 (14.8-30.2)

Abbreviations: BTK, Bruton's tyrosine kinase; allo-HSCT, allogeneic hematopoietic stem cell transplantation; auto-HSCT, autologous hematopoietic stem cell transplantation; CAR-T, chimeric antigen receptor T-cell therapy; GMT, geometric mean titer; CI, confidence interval

Blood draws were conducted prior to and after vaccine dose three.

[a]All lab assessments were within 3 months before dose three of the vaccine. 17.6% of total patients had missing lymphocyte count. Among patients with plasma cell disorder, 3.8% had missing IgG values, 3.8% had missing IgA values, and 3.8% had missing IgM values.

[b]Anti-androgen and anti-estrogen hormonal therapies were not considered anticancer therapy for this study.

[c]Small molecules include tyrosine kinase inhibitors, proteasome inhibitors, lenalidomide, pomalidomide, and venetoclax.

[d]As this sub-analysis group only included one patient, a confidence interval cannot be generated.

**P*-values were calculated comparing patients on a specific therapy with patients not on the therapy on a specific study time point by Fisher exact test or Chi-square test (antibody seropositivity 29 days after dose 3).

***P*-values were calculated by comparing patients on a specific therapy with those not on the therapy on a specific study time point by the Kruskal-Wallis test (GMTs 29 days after dose 3).

¶*P*-values were calculated by comparing hematological malignancies with solid tumors

[#] *P*-values were calculated comparing myeloid, lymphoid, and plasma cell disorders.

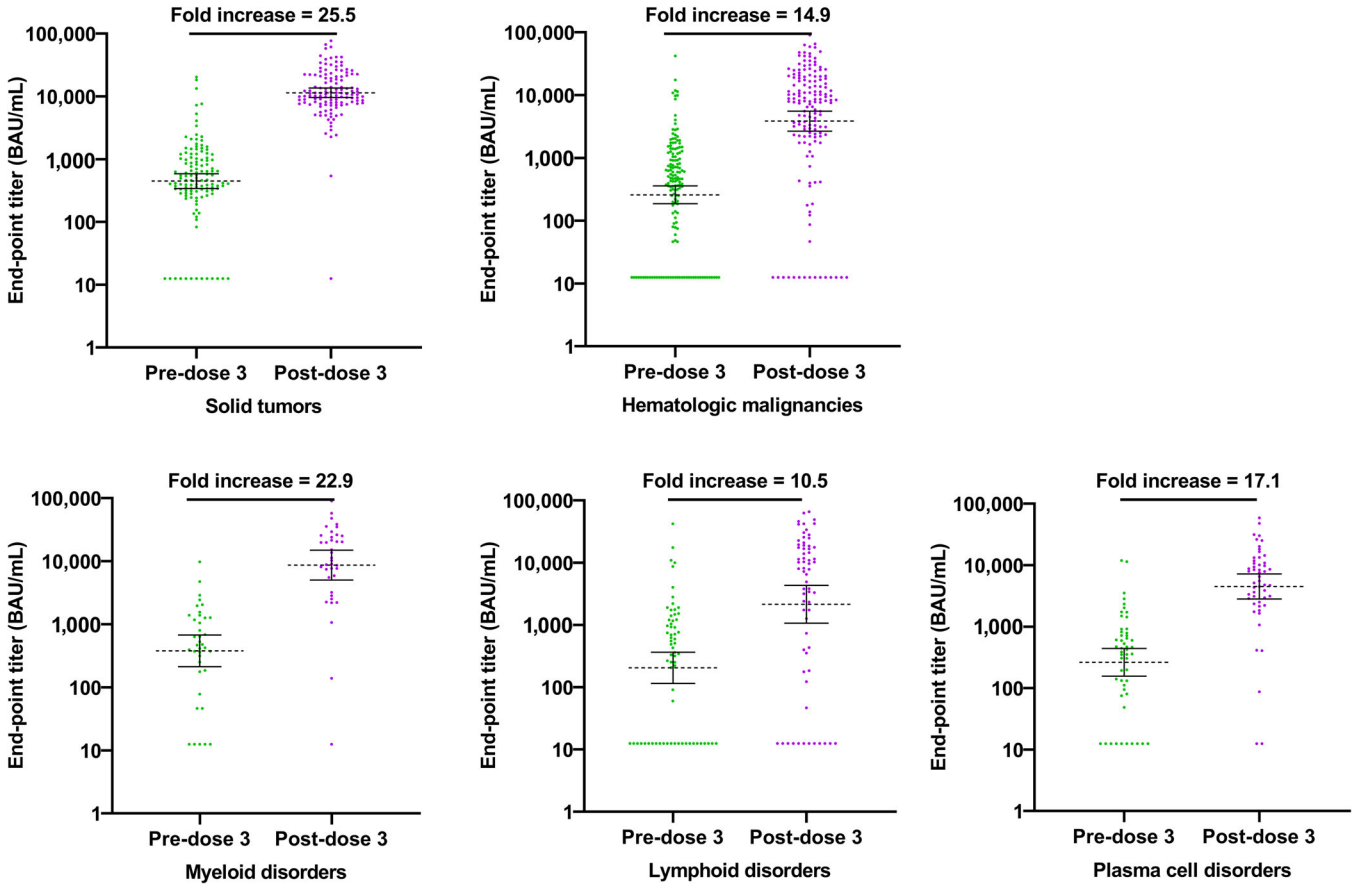

FIGURE 1 Comparison of antibody titers (ELISA) pre-dose 3- and one-month post-dose 3 by cancer type and type of hematological malignancy.

Abbreviations: ELISA, enzyme-linked immunosorbent assay; HM, hematological malignancy.

TABLE 4 Percent SARS-CoV-2 antibody seropositive (95% CI) at each timepoint pre- and post-doses 1, 2, and 3 of the mRNA-1273vaccine by cancer patient category among patients in the subcohort (Cohort 1) ($n = 130$).

Characteristics	Pre-Dose 1	Post-Dose 1	Post-Dose 2	Pre-dose 3	Post-dose 3	*n*
Overall	0.8 (0.0-4.2)	71.5 (63.0-79.1)	90.8 (84.4-95.1)	84.6 (77.2-90.3)	95.4 (90.2-96.3)	130
Tumor type						
Hematologic malignancies	1.2 (0.0-6.6)	58.5 (47.1-69.3)	85.4 (75.8-92.2)	79.3 (68.9-87.4)	92.7 (84.8-97.3)	82
Myeloid disorders	0.0	36.8 (16.3-61.6)	100.0 (82.4-100.0)	94.7 (74.0-99.9)	100.0 (82.4-100.0)	19
Lymphoid disorders	2.9 (0.1-14.9)	57.1 (39.4-73.7)	68.6 (50.7-83.1)	65.7 (47.8-80.9)	82.9 (66.4-93.4)	35
Plasma cell disorders	0.0	75.0 (55.1-89.3)	96.4 (81.7-99.9)	85.7 (67.3-96)	100.0 (87.7-100.0)	28
Solid tumor	0.0	93.8 (82.8-98.7)	100.0 (92.6-100.0)	93.8 (82.8-98.7)	100.0 (92.6-100.0)	48

the percentage of seropositive patients (Table 4) and the GMTs increased with administration of each additional vaccine dose (Table 5, Figure 2). Vaccine dose three significantly increased GMTs compared to pre-dose three levels and led to significantly increased GMTs over what was achieved after two vaccine doses. Although GMTs dropped nearly 3-fold in the ~7 to 9 months between doses two and three, administration of dose three resulted in titers that were considerably higher 28 days after dose three compared to 28 days post–dose two (ranging from 3.7- to 9.6-fold higher). Titers among lymphoid cancer patients, who had the lowest response to the vaccine, increased 4.7-fold between post–dose two and post–dose three.

TABLE 5 SARS-CoV-2 antibody geometric mean titers, AU/mL (95%CI) at each timepoint pre- and post-doses 1, 2, and 3 of the mRNA-1273 by cancer patient category among patients in the subcohort (Cohort 1) ($n = 130$).

	Vaccine dosing						
Characteristics	**Pre-Dose 1**	**Post-Dose 1**	**Post-Dose 2**	**Pre-dose 3**	**Post-dose 3**	**Fold increase post-dose 3 to post-dose 2[a] (95% CI)**	**Fold increase post-dose 3 to pre-dose 3[b] (95% CI)**
Overall	13.0 (12.1-13.9)	102.5 (75.6-139.0)	1,129.4 (801.0-1,592.5)	364.2 (266.8-497.2)	5,962.0 (4,335.2-8,199.2)	5.3 (4.2-6.7)	16.4 (12.8-21.0)
Tumor type							
Hematologic malignancies	13.2 (11.8-14.8)	68.0 (45.7-101.2)	784.8 (474.7-1,297.4)	297.1 (191.8-460.3)	4,007.4 (2,493.2-6,441.3)	5.1 (3.7-7.1)	13.5 (9.7-18.7)
Myeloid disorders	12.5 [c]	39.1 (16.7-91.9)	1,009.3 (406.5-2,506.1)	479.3 (241.3-952.0)	9,682.5 (5,888.4-15,921.3)	9.6 (3.9-23.4)	20.2 (10.8-37.7)
Lymphoid disorders	14.3 (10.9-18.8)	62.9 (32.2-122.8)	376.7 (150.7-941.9)	206.5 (92.1-463.2)	1,786.1 (677.1-4,711.6)	4.7 (2.8-8.1)	8.6 (5.0-14.9)
Plasma cell disorders	12.5 [c]	109.1 (59.3-200.6)	1,656.1 (842.1-3,257.0)	338.5 (168.4-680.5)	6,047.7 (3,661.5-9,988.9)	3.7 (2.5-5.4)	17.9 (10.5-30.3)
Solid tumors	12.5 [c]	206.5 (136.1-313.1)	2,103.3 (1,547.8-2,858.2)	515.7 (349.4-761.2)	11,752.1 (9,632.6-14,338.0)	5.6 (4.2-7.5)	22.8 (15.7-33.1)

Abbreviations: GMT, geometric mean titer.
[a]Fold rise in GMTs was calculated by comparing post-dose 3 GMTst o post-dose 2 GMTs.
[b]Fold rise in GMTs was calculated by comparing post-dose 3 GMTs to pre-dose 3 GMTs.
[c]The GMTs were below the level of detection and have been assigned a value of 12.5. The 95% CI cannot be calculated if they are the same values.

FIGURE 2 Antibody titers over time among cancer patients in the subcohort evaluated after each vaccine dose (Cohort 1) ($n = 130$)

Fifty-two patients were SARS-CoV-2 antibody seronegative prior to dose three; of them, 36 (69.2%) seroconverted after dose three, while 16 (30.8%) did not. Notably, patients' median age, racial/ethnic background, disease status, IgG, IgA, and IgM levels, receipt of anticancer therapy (chemo-, immune-, and radiation therapy) within three months, small molecules, cellular therapy, anti-CD38 antibodies within six months, BTK inhibitor, or line of systemic therapy to date were comparable between these two subgroups Supplementary Table S1). The differences reaching statistical significance between these 2 groups were that a higher proportion of non-seroconverting patients had been treated with anti-CD20 antibodies within the last six months (71.4%% and 24.4%, respectively), and a higher proportion of non-seroconverting patients had hematologic malignancies than solid tumors (38.5% and 7.7%, respectively). The GMT of the 36 patients who seroconverted increased from 12.5 AU/mL prior to dose three to 1906.5 AU/mL after dose three, a ~153-fold increase. The GMTs were considerably higher among the pre-dose three positive patients ($n = 232$), resulting in a strong but lower fold increase of 16.8 (687.3 and 11565.1 AU/mL, pre- and post-dose three, respectively) compared to the pre-dose three seronegative patients (data not shown)

Of the 16 patients who remained seronegative at day +28 after receipt of dose three, 15 had HM (1 myeloid disorder, 12 lymphoid disorders, and 2 plasma cell disorders), and 1 was a solid tumor patient (Supplementary Table S1). Ten were in remission, while 6 had relapsed, refractory, or stable disease. The total lymphocyte count was lower among those who did not seroconvert after dose three, with 12 of the patients having a count $\leq 1 \times 10^9$ mL within three months prior to dose three.

4 | DISCUSSION

This is one of the largest studies to report on the administration of dose three of the mRNA-1273 COVID-19 vaccine to cancer patients. The data reported here suggest that receipt of vaccine dose three is particularly beneficial to cancer patients, especially those with hematologic malignancies, most notably lymphoid cancer. Four weeks after dose three of mRNA-1273, most patients showed a robust response to the vaccine, with titers increasing 10.5- to 25.5-fold depending on the type of cancer with which they were diagnosed.

Assessment of the antibody response after vaccine dose three by cancer type yielded several important additional observations. First, among the small subset of patients who had no detectable antibodies prior to dose three, nearly 70% seroconverted after vaccine dose three. Administration of dose three not only led to seroconversion among those with nondetectable antibody titers prior to dose three but also led to substantially higher titers than observed after the second vaccine dose. Second, patients with HM had lower antibody titers compared to those with solid tumors, aligning with other data suggesting that vaccine responses are often diminished in patients with HM as a result of B-cell defects [13, 14]. Third, antibody responses after dose three were reduced in those with lower total lymphocyte counts ($\leq 1 \times 10^9$ mL) as well as those who had received anticancer therapy within 3 months (specifically anti-CD20, CD38, and BTK inhibitors). A similar blunting of antibody response was previously observed based on the type of therapy following the two-dose primary series as well [2]. Finally, and perhaps most importantly, despite waning humoral immunity observed following the second vaccine dose, administration of vaccine three dose restored antibody titers to higher levels than were observed following the second vaccine dose, even among lymphoid cancer patients (who had the lowest and slowest humoral response after each vaccine dose), suggesting good immunologic memory. Several of these observations have also been corroborated by other recent studies, in which a majority of HM patients who were seronegative prior to dose 3 seroconverted following dose 3 and in which BTK inhibitors and anti-CD20 treatments were associated with a blunted humoral response to dose three [7, 15].

Among lymphoid cancer patients, the frequent and standard usage of B-cell–depleting therapies likely explains the dampened humoral response to the mRNA-1273 vaccine. In addition, such therapies are administered chronically (e.g., BTK inhibitors) or have very long-acting B-cell depleting properties (e.g., anti-CD20 antibodies), making it likely that a majority of patients with advanced lymphoid cancers will experience a less robust humoral response to COVID-19–directed vaccines. Interestingly, T-cell immune responses may occur in a minority of patients lacking a humoral response following the initial 2-dose COVID-19 vaccine series, yet the cellular response following vaccine dose three in such patients remains to be determined [16, 17].

This study is one of the largest to report on safety following COVID-19 vaccine dose three in cancer patients. Dose three of mRNA-1273 in this population of cancer patients was well tolerated. Adverse reactions, consisting primarily of injection site reactions, fever and fatigue, were similar to those reported after two vaccine doses in this same population [2] and were generally similar to the adverse event profile observed in healthy adults after the first and second doses and after a booster dose [18–21]. Notably, the vast majority (90%) of treatment-emergent adverse events occurred within 14 days (+5) of vaccine administration, whereas severe adverse events were extremely rare at either timepoint assessed, suggesting a low risk for significantly delayed toxicities. Our safety results also appear concordant with those observed in other small series of patients with cancer or immunocompromised states (e.g., post-allogeneic transplantation) [22, 23]. However, the data suggest that longer-term follow-up following vaccine dose three will be necessary to fully annotate the toxicity in this population.

The use of a binding assay (enzyme-linked immunosorbent assay [ELISA]) as opposed to a neutralization assay limited our ability to determine functional immunity derived from vaccine dose three. Recent evidence, however, suggests that neutralizing antibody response occurs among cancer patients following vaccine dose three, including in patients with undetectable neutralizing antibodies after 2 doses [15]. There were several other limitations of our study as well. First, we did not determine immunogenicity against different variants, including current circulating sub-variants of Omicron. Second, because vaccine efficacy was not directly assessed in this study and no immune correlate of protection has been identified, we cannot infer protection following dose three based on the titers observed in this study. While a protective effect following a 2-dose regimen in cancer patients has been observed [24], and a recent observational study also suggested a clinically protective effect following dose three in cancer patients [25], threshold levels of antibody titers associated with protection remain to be determined. Third, the number of patients in each category receiving specific therapies was lower for some analyses, thereby limiting our ability to draw firm conclusions about vaccine responses in certain patient subsets. Finally, the recommendation to administer vaccine dose three as part of

the priming series for immunocompromised individuals as soon as 28 days after the second dose differs from the duration between doses in this study. As such, the immune responses observed in standard clinical practice may differ from those reported here. Important strengths of this research include the large sample size, diverse population of cancer patients with various underlying conditions and cancer therapy received, and the ability to follow a large cohort of 130 subjects through three successive vaccine doses.

The results of this study highlight the value of a three-dose primary series for cancer patients, as currently recommended by the Advisory Committee on Immunization Practices (ACIP) [26, 27]. Timely receipt of all three doses for patients with HM, especially those receiving immunosuppressive therapy and those with significantly waned or absent humoral immunity prior to dose three, is supported by our findings. The implications of failure to seroconvert following dose three are unclear, but it would seem reasonable to strongly consider such patients for passive immunization or other preventive approaches. With the arrival of variants of concern, including Omicron, the ACIP has further revised its recommendations to administer a fourth and fifth dose for immunocompromised patients. Further research is needed to determine the best timing for vaccine receipt among cancer patients in relation to their cancer therapy regimen, the appropriate interval between doses to obtain the optimal immune response, and the ultimate clinical efficacy of additional vaccine doses in cancer patients.

DECLARATIONS

AUTHOR CONTRIBUTIONS

Conceptualization: Anna Giuliano, Jeffrey Lancet, Patrick Hwu, Brett Leav, Barbara Kuter; Methodology: Anna Giuliano, Jeffrey Lancet, Junmin Whiting, Qianxing Mo; Formal analysis: Junmin Whiting, Qianxing Mo, Christopher Cubitt; Investigation: Anna Giuliano, Jeffrey Lancet, Shari Pilon-Thomas, Junmin Whiting, Christopher Cubitt, Christopher Dukes, Kimberly Isaacs-Soriano, Kayoko Kennedy, Somedeb Ball, Ning Dong, Akriti Jain; Resources: Shari Pilon-Thomas, Christopher Cubitt; Writing – Original Draft: Anna Guiliano, Jeffrey Lancet, Barbara Kuter; Writing – Review and Editing: Jeffrey Lancet, Anna Giuliano, Junmin Whiting, Quanxing Mo, Brett Leav, Bradley Sirak, Christopher Cubitt, Kimberly Isaacs-Soriano, Kayoko Kennedy, Patrick Hwu; Visualization: Jeffrey Lancet, Anna Giuliano, Junmin Whiting, Christopher Cubitt, Kimberly Isaacs-Soriano, Kayoko Kennedy; Supervision: Anna Giuliano, Jeffrey Lancet; Project administration: Anna Giuliano, Jeffrey Lancet, Bradley Sirak; Funding acquisition: Anna Giuliano.

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ETHICS APPROVAL STATEMENT

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Advarra Institutional Review Board (IRB# 00000971). All the participants provided written informed consent before enrollment in this study. This study followed the STrengthening the Reporting of OBservational Studies in Epidemiology (STROBE) reporting guidelines.

CONFLICT OF INTEREST STATEMENT

Brett Leav is an employee of Moderna and holds shares in Moderna; Barbara Kuter is a consultant of Moderna; Jeffrey Lancet and Anna Giuliano received research funding from Moderna. All other authors report no conflicts of interest.

FUNDING INFORMATION

Research funding was provided by Moderna.

PATIENT CONSENT STATEMENT

All patients provided written informed consent prior to enrollment in the study.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Christopher Dukes https://orcid.org/0000-0002-6322-1834

Jeffrey Lancet https://orcid.org/0000-0002-7751-7310

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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