Immunogenicity and Reactogenicity of SARS-CoV-2 Vaccines in Patients With Cancer: The CANVAX Cohort Study

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PURPOSE The immunogenicity and reactogenicity of SARS-CoV-2 vaccines in patients with cancer are poorly understood.

METHODS We performed a prospective cohort study of adults with solid-organ or hematologic cancers to evaluate anti–SARS-CoV-2 immunoglobulin A/M/G spike antibodies, neutralization, and reactogenicity ≥7 days following two doses of mRNA-1273, BNT162b2, or one dose of Ad26.COV2.S. We analyzed responses by multivariate regression and included data from 1,638 healthy controls, previously reported, for comparison.

RESULTS Between April and July 2021, we enrolled 1,001 patients; 762 were eligible for analysis (656 had neutralization measured). mRNA-1273 was the most immunogenic (log10 geometric mean concentration [GMC] 2.9, log10 geometric mean neutralization titer [GMT] 2.3), followed by BNT162b2 (GMC 2.4; GMT 1.9) and Ad26.COV2.S (GMC 1.5; GMT 1.4; P < .001). The proportion of low neutralization (< 20% of convalescent titers) among Ad26.COV2.S recipients was 69.9%. Prior COVID-19 infection (in 7.1% of the cohort) was associated with higher responses (P < .001). Antibody titers and neutralization were quantitatively lower in patients with cancer than in comparable healthy controls, regardless of vaccine type (P < .001). Receipt of chemotherapy in the prior year or current steroids were associated with lower antibody levels and immune checkpoint blockade with higher neutralization. Systemic reactogenicity varied by vaccine and correlated with immune responses (P = .002 for concentration, P = .016 for neutralization). In 32 patients who received an additional vaccine dose, side effects were similar to prior doses, and 30 of 32 demonstrated increased antibody titers (GMC 1.05 before additional dose, 3.17 after dose).

CONCLUSION Immune responses to SARS-CoV-2 vaccines are modestly impaired in patients with cancer. These data suggest utility of antibody testing to identify patients for whom additional vaccine doses may be effective and appropriate, although larger prospective studies are needed.
people age older than 65 years. Some studies have suggested lower seroconversion rates and antibody concentrations following SARS-CoV-2 vaccination in patients with cancer, and particularly low responses in patients who have received B-cell–depleting agents. However, these studies are limited in size, thereby prohibiting key subgroup analyses, and frequently report only measurement of binding antibodies, or focus on the effects of individual vaccines.

We aimed to identify correlates of the immunogenicity and reactogenicity of current US Food and Drug Administration Emergency Use Authorization vaccines in a large cohort of approximately 1,000 patients enrolled in the Cancer, COVID, and Vaccination (CANVAX) study.

METHODS
Study Design, Eligibility, and Study Procedures
The CANVAX study is a prospective cohort study that enrolled adult patients at the Massachusetts General Hospital Cancer Center who intended to receive or had received SARS-CoV-2 vaccination. The study was advertised on a website and on posters across the cancer center; patients were also directly referred by their oncology care team. Written informed consent was obtained. Participants completed a standardized electronic or paper questionnaire that included questions about baseline demographics, cancer treatment history, medical history, SARS-CoV-2 exposures and infection, vaccination information, and postvaccine symptoms (vaccine reactogenicity). Additional clinical information was abstracted from the medical record, including cancer type, cancer history, complete blood counts obtained at the last visit before vaccination, cancer therapy within 1 year before enrollment, or contemporaneous corticosteroid use (excluding replacement dose or chemotherapy-associated dosing).

This analysis considers CANVAX participants with completed baseline survey and antibody testing from April 21 through July 21, 2021; or with antibody testing after an additional vaccine dose through September 20, 2021. We excluded individuals who had been sampled within 7 days of the final dose of the vaccine series or had not completed the full series. The results of antibody testing at the primary timepoint were returned to participants. This study was approved by the Mass General Brigham Human Research Committee (2021P000746).

Data from healthy controls recruited into a separate study in Chelsea or Boston, Massachusetts, and analyzed contemporaneously (detailed elsewhere) are included as healthy (noncancer) comparison cohorts.

Antibody Assays
Serum antibody assays were performed with the Roche Elecsys Anti–SARS-CoV-2 S assay (Roche Diagnostics, Indianapolis, IN), at the Massachusetts General Hospital Core Clinical laboratory, a CLIA laboratory. Participants with a negative test result (cutoff index < 0.4) were offered confirmatory testing 7-14 days later and referred to clinical immunology specialists for further counseling at the discretion of the treating oncologist. A positive anti-nucleocapsid antibody (Roche Elecsys Anti–SARS-CoV-2 total [nucleocapsid assay]) was regarded as evidence of prior infection.

Assessment of Neutralization
Neutralization was measured with a SARS-CoV-2 pseudovirus neutralization assay that has been previously described. A pseudovirus neutralization titer 50 was calculated by taking the inverse of the serum concentration that achieved 50% neutralization of SARS-CoV-2 pseudotyped lentivirus particles entry into cells.

Study End Point and Statistical Analysis
The primary end points of this study were immunoglobulin (Ig)A/G/M antispike antibody concentration and neutralization titers. Secondary end points included reactogenicity.
A prespecified enrollment target of 1,000 was designated, and analyses according to vaccine, cancer type, treatment type, and age were prespecified. A copy of the study protocol is available from the authors. Analyses were performed in R (v4.0.5) using the gtsummary packages and glm() and glm(family = binomial) functions. We modeled log_{10}-transformed antispike concentration or pseudovirus neutralization titer 50 as the dependent variable, and age, sex, ethnicity, days postvaccination, vaccine group, prior infection, cancer type, therapy type, and steroids as the independent variables. All \( P \) values reported are adjusted (ie, multivariate) except in Tables S1, S7, and S8 in the Data Supplement (online only), where they represent simple Fisher’s exact or chi-squared test results. Figures were rendered in GraphPad Prism v9.0.

RESULTS

Patient Characteristics

Between April 29 and July 20, 2021, 1,622 patients were screened for enrollment (Data Supplement) and 1,001 were enrolled. In total, 762 were eligible for the current analysis. Between April 29 and July 20, 2021, 1,622 patients were enrolled. In total, 762 were eligible for the current analysis.

The overall proportion of asymptomatic, antibody-positive patients included in this cohort are summarized in Table 1. Of note, 9% of the cohort was non-White and 2.2% self-identified as Hispanic or Latinx. Seventy-one-and-one-half percent (71.5%) of the cohort received care primarily for cancer-directed systemic therapy. 37.8% (288 of 762) of the participants had completed a vaccine series with mRNA-1273 (two doses), 50.3% with BNT162b2 (two doses), and 11.9% with Ad26.COV2.S (single dose). Details for each group are included in the Data Supplement. Participants were sampled at a median of 79 days (interquartile range [IQR], 57–106 days) after the first dose of vaccine.

Prevalence of Antibody-Confirmed Prior SARS-CoV-2 Infection

Among the 7% (53 of 762) of participants with a positive antinucleocapsid antibody result indicating prior SARS-CoV-2 infection, 71.7% (38 of 53) reported that they had a known history of SARS-CoV-2 infection, of whom 18.4% (7 of 38) had been hospitalized and 13.2% (5 of 38) were asymptomatic. The overall proportion of asymptomatic, antibody-confirmed SARS-CoV-2 infection was 30.2% (16 of 53). Ten participants reported a prior history of SARS-CoV-2 infection but had undetectable nucleocapsid antibodies; their vaccine responses were similar to individuals without prior infection and they are analyzed as nucleocapsid antibody negative.

Immunogenicity of SARS-CoV-2 Vaccines

Antibody responses to current US Food and Drug Administration Emergency Use Authorization SARS-CoV-2 vaccines are directed against the spike protein. We analyzed combined antispike IgA/G/M antibody concentrations and neutralization titers. For comparison, we included data using the same assays in a healthy (noncancer) cohort of 418 (supplemented further with 1,220 prepandemic controls for neutralization assay validation) healthy ambulatory adults collected contemporaneously and previously described.19 In the primary multivariate analysis of antibody concentration and neutralization titers, vaccine type, prior infection, treatment modalities, cancer type, age, and time of sampling are independently associated (Table 2). We present exploration of each correlate below.

Vaccine type and prior infection. Antibody concentrations and neutralization titers differed significantly according to vaccine with responses to mRNA-1273 being the highest (geometric mean antibody concentration in log_{10} U/mL [GMT] 2.9; geometric mean neutralization titer in log_{10} units [GMT] 2.3), followed by BNT162b2 (GMT 2.4; GMT 1.9) and finally Ad26.COV2.S (GMT 1.5; GMT 1.4) (Fig 1, Table 2; multivariate adjusted \( P < .001 \)). Seroconversion rates (ie, a positive spike antibody above the threshold for positivity of 0.8 U/mL) followed a similar pattern. Quantitative antibody concentrations and neutralization titers were lower in patients with cancer in CANVAX compared with healthy (noncancer) controls, even after adjusting for age, time of sampling, and vaccine (antibody concentrations: –0.6 log_{10} U/mL; 95% CI, –0.80 to –0.41; \( P < .001 \); neutralization titer: –0.35 log_{10} U/mL; 95% CI, –0.06 to –0.03; \( P < .001 \); Data Supplement). A propensity-score matching approach yielded similar results (Data Supplement) and highlights the higher immunogenicity of mRNA vaccines compared with Ad26.COV2.S (Data Supplement). Prior SARS-CoV-2 infection was associated with significantly higher antibody titers and neutralization (Fig 1 and Table 2), as has been observed in noncancer patients.19,21 Relative to unvaccinated healthy (noncancer) controls with prior infection, responses among vaccinated CANVAX patients with prior infection were higher regardless of vaccine, and among those without prior infection, responses were higher after mRNA1273, similar after BNT162b2 and lower after Ad26.COV2.S (Data Supplement).

Therapy and cancer types. Receipt of chemotherapy in the preceding 12 months was associated with lower antibody concentrations (–0.29 log_{10} U/mL; 95% CI, –0.44 to –0.14; \( P < .001 \)) and neutralization titers (–0.21; 95% CI, –0.32 to –0.09; \( P < .001 \); Fig 2; Table 2). There was no statistical heterogeneity in effect by time of chemotherapy administration (1 month, 1-3 months, and 3-12 months; interaction \( P > .05 \)). In a nonprespecified analysis in 458 individuals with blood counts available, lymphopenia (absolute lymphocyte count< 1,000/μL), measured at the last visit before vaccination (median of 6 days prior, IQR 19.0 days), was associated with lower antibody concentrations (–0.26 log_{10} U/mL; 95% CI, –0.46 to –0.06; \( P = .01 \)), but not neutralization titers. Neither absolute neutrophil count nor neutropenia (absolute
TABLE 1. Baseline Characteristics of the Cancer, COVID, and Vaccination Cohort (N = 762) and the Healthy (noncancer) Control Cohort (Reported in Ref. 19)

| Characteristic                                    | N = 762 | N = 418 |
|--------------------------------------------------|---------|---------|
| Age, years (IQR)                                 | 66 (56-73) | 43 (31-54) |
| Sex, No. (%)                                      |         |         |
| Female                                           | 471 (62) | 227 (54) |
| Male                                             | 290 (38) | 191 (46) |
| Other                                            | 1 (0.1)  | 0 (0)   |
| Ethnicity, No. (%)                               |         |         |
| Hispanic or Latinx                               | 17 (2.2) | 246 (58.9) |
| Not Hispanic or not Latinx                       | 685 (90) | 167 (40) |
| Unavailable or choose not to provide             | 60 (7.9) | 5 (1.2) |
| Race, No. (%)                                     |         |         |
| American Indian or Alaska Native                 | 0 (0)   |         |
| Asian                                            | 35 (4.6) |         |
| Black                                            | 8 (1.0)  |         |
| Native Hawaiian or Pacific Islander              | 3 (0.4)  |         |
| White                                            | 694 (91) |         |
| More than one race                                | 1 (0.1)  |         |
| Unavailable or choose not to provide             | 21 (2.8) |         |
| Cancer type, No. (%)                             |         |         |
| Solid organ (n = 545; 71.5%)                     |         |         |
| Thoracic*                                        | 193 (25) |         |
| Breast                                           | 193 (25) |         |
| Melanoma or Merkel cell cancer                   | 87 (11)  |         |
| Head and neck                                    | 59 (7.7) |         |
| GI                                               | 22 (2.9) |         |
| Other                                            | 19 (2.5) |         |
| Hematologic (n = 198; 26%)                       |         |         |
| Bone marrow transplanted*                        | 113 (15) |         |
| Leukemia                                         | 52 (6.8) |         |
| Myeloproliferative neoplasm or myelodysplastic syndrome | 18 (2.3) |         |
| Lymphoma                                         | 6 (0.8)  |         |
| Other                                            | 19 (2.5) |         |
| Stage (most recent), No. (%)                     |         |         |
| 1                                                | 76 (12)  |         |
| 2                                                | 68 (11)  |         |
| 3                                                | 75 (12)  |         |
| 4                                                | 226 (36) |         |
| Nonstageable disease*                            | 184 (29) |         |
| Therapy in the prior 12 months, No. (%)          |         |         |
| No systemic therapy                              | 205 (27) |         |
| Chemotherapy                                     | 101 (13) |         |
| Immune checkpoint blockade                       | 70 (9.2) |         |
| Targeted therapy                                 | 149 (20) |         |
| Combination                                      | 124 (16) |         |
| Receiving corticosteroids*                       | 70 (9.2) |         |

Abbreviation: IQR, interquartile range.

*Includes lung cancer, thymic cancers, and mesothelioma.

†Includes four chimeric antigen receptor T-cell recipients.

‡Includes patients not eligible for staging, for example, myelodysplastic syndrome or bone marrow transplant.

§Corticosteroids at doses above replacement doses and excluding administration around chemotherapy.

neutrophil count < 1,500/mL was associated with antibody concentrations.

Receipt of immune checkpoint blockade tended to be associated with higher neutralization titers (0.13; 95% CI, -0.01 to 0.27; P = .063; Fig 2; Table 2). Current receipt of corticosteroids was associated with lower antibody concentrations (-0.37; 95% CI, -0.61 to -0.12; P = .003) and tended to be associated with lower neutralization titers (-0.15; 95% CI, -0.33 to 0.03; P = .09; Data Supplement). There were no significant differences in antibody concentration or neutralization titers between tumor types among patients with solid tumors, but responses were lower in patients who had undergone bone marrow transplantation (Data Supplement) or with hematologic malignancies.

**Age and time of sampling.** Increasing age was associated with lower antibody concentration and neutralization titers (P < .001 for both comparisons; Data Supplement). Later sampling relative to vaccination was associated with significantly lower neutralization titers, and modeling these cross-sectional measures suggested a linear decay (Data Supplement).

**Correlates of low neutralization.** Antibody levels and neutralization titers correlate with protection against infection in animal models and clinical trials of vaccines. There is, as yet, no specific threshold indicative of protection but a neutralization titer > 20% of the GMT in convalescent individuals (a value of 27.6 in this study) corresponds with 50% reduction in infection risk in modeling studies. Overall, 18.7% of patients with cancer who received mRNA-1273, 34.7% who received BNT162b2, and 69.9% who received Ad26.COV2.S had neutralization titers lower than this level (Fig 1). Receipt of Ad26.COV2.S (odds ratio [OR] 11.3; 95% CI, 6.04 to 21.6 relative to mRNA-1273; P < .001), BNT162b2 (OR 2.47; 95% CI, 1.63 to 3.82 relative to mRNA-1273; P < .001), hematologic malignancy (OR 1.57; 95% CI, 1.05 to 2.35; P = .028), and age (OR 1.12 per 5-year increase; 95% CI, 1.04 to 1.21; P = .002) were associated with increased odds of having a low neutralization titer < 27.6 (Data Supplement). Prior SARS-CoV-2 infection (OR 0.14; 95% CI, 0.03 to 0.42; P = .002) and receipt of immune checkpoint blockade (OR 0.47; 95% CI, 0.27 to 0.80; P = .002) were associated with reduced odds.

**Reactogenicity of SARS-CoV-2 Vaccines in Patients With Cancer**

We assessed local and systemic adverse effects after vaccination. The majority of participants, 71.5% (545 of 762), reported at least one local or systemic symptom after vaccination (Data Supplement). The most frequent local symptom was pain at the site of injection (Data Supplement; Fig 3). The timing of local symptoms was most frequently after both doses of vaccine, or after the second dose only (in mRNA vaccine recipients). The most common systemic symptom was fatigue. Systemic symptoms were

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most commonly seen after the second dose of vaccine. The frequency of local or systemic symptoms was highest in mRNA-1273 recipients (81%, 233 of 288), followed by BNT162b2 recipients (72%, 274 of 383) and lowest in Ad26.COV2.S recipients (42%, 38 of 91) (P < .001; Data Supplement). Most patients reported their symptoms were mild or moderate (89%, 479 of 538). Prior infection was associated with higher systemic, but not local, symptoms (Data Supplement).

Association Between Reactogenicity and Immunogenicity of SARS-CoV-2 Vaccines

As reactogenic symptoms may be because of immune mechanisms involved in vaccine immunogenicity, we hypothesized that reactogenicity may associate with immunogenicity. Adjusting for vaccine type and prior infection, the presence of systemic symptoms was associated with higher antibody concentration (0.23 log_{10} U/mL higher; CI, 0.08 to 0.39; P = .002) and neutralization titers (0.14 log_{10} higher; 0.03 to 0.25; P = .016; Fig 3 and the Data Supplement). No association between local symptoms and immune responses was observed.

Responses to Additional Vaccine Doses

The safety and immune response to additional vaccine doses given after the full series of vaccines is not known. Thirty-two participants reported receiving either the mRNA-1273 (n = 15) or BNT162b2 (n = 17) vaccine following completion of the mRNA-1273 (n = 7), BNT162b2 (n = 17), or Ad26.COV2.S (n = 8) series, either on the recommendation of their medical team, or following recent CDC guidance (September 12, 2021). One participant each reported receiving two additional doses of mRNA-1273 or BNT162b2, and are included in the analysis below.

| Characteristic                  | Spike (n = 762) | Neutralization (n = 655) |
|---------------------------------|----------------|-------------------------|
|                                 | Effect Size (log_{10} U/mL) | 95% CI | Adjusted P | Effect Size (pNT50 U/mL) | 95% CI | Adjusted P |
| Age (per 5 years)               | -0.06          | -0.09 to -0.03          | < .001   | -0.04          | -0.06 to -0.03          | < .001   |
| Sex                             |                |                        |          |                |                        |          |
| Female                          | Ref.           |                        |          | Ref.           |                        |          |
| Male                            | -0.07          | -0.22 to 0.08          | .4       | 0              | -0.12 to 0.11          | > .9     |
| Ethnicity                       |                |                        |          |                |                        |          |
| Hispanic or Latinx              | Ref.           |                        |          | Ref.           |                        |          |
| Not Hispanic or not Latinx      | 0.05           | -0.43 to 0.53          | .8       | -0.35          | -0.72 to 0.02          | .065     |
| Prior infection (serology)      |                |                        |          |                |                        |          |
| Negative                        | Ref.           |                        |          | Ref.           |                        |          |
| Positive                        | 1.2            | 0.88 to 1.4            | < .001   | 1              | 0.79 to 1.2            | < .001   |
| Vaccine                         |                |                        |          |                |                        |          |
| mRNA1273                        | Ref.           |                        |          | Ref.           |                        |          |
| BNT162b                         | -0.51          | -0.66 to -0.36         | < .001   | -0.45          | -0.56 to -0.34         | < .001   |
| AD26.COV2.S                     | -1.3           | -1.5 to -1.0           | < .001   | -0.94          | -1.1 to -0.76          | < .001   |
| Cancer type                     |                |                        |          |                |                        |          |
| Solid                           | Ref.           |                        |          | Ref.           |                        |          |
| BMT                             | -0.32          | -0.53 to -0.11         | .003     | -0.09          | -0.24 to 0.07          | .3       |
| Hematologic cancer              | -0.49          | -0.73 to -0.25         | < .001   | -0.32          | -0.50 to -0.14         | < .001   |
| Receiving chemotherapy          | -0.29          | -0.44 to -0.14         | < .001   | -0.21          | -0.32 to -0.09         | < .001   |
| Receiving immune checkpoint blockade | 0.05       | -0.14 to 0.25         | .6       | 0.13           | -0.01 to 0.27         | .063     |
| Receiving targeted therapy      | -0.01          | -0.17 to 0.15          | > .9     | 0.05           | -0.07 to 0.17          | .4       |
| Concurrent corticosteroids       |                |                        |          |                |                        |          |
| Not receiving corticosteroids   | Ref.           |                        |          | Ref.           |                        |          |
| Receiving corticosteroids       | -0.37          | -0.61 to -0.12         | .003     | -0.15          | -0.33 to 0.03          | .092     |
| Time (per week after 1st dose)  | 0              | -0.01 to 0.02          | 0.7      | -0.03          | -0.05 to -0.02         | < .001   |

NOTE. Shown are the results of multivariate regression model including the covariates shown, with either antispike immunoglobulin A/G/M or SARS-CoV-2 neutralization as the response variable.

Abbreviations: BMT, bone marrow transplant; pNT50, pseudovirus neutralization titer 50.
FIG 1. Immunogenicity of mRNA-1273, BNT-162b2, and Ad26.COV2.S in CANVAX participants. (A) The quantitative SARS-CoV-2 spike IgG/A/M antibody concentration (Roche Elecsys Anti–SARS-CoV-2 assay) in U/mL of serum for 762 CVX and 418 HCs included for interpretation. Individual measures are grouped by antibody-confirmed prior infection and vaccine. Total antispike (IgA/M/G) antibody concentrations > 2,500 U/mL triggered additional manual dilution (where sample availability allowed) to yield titers up to 250,000 U/mL. An antibody cutoff index (COI) > 0.8 was defined as positive (dotted line). All assays were run blinded to clinical information. The number (continued on following page)
We measured responses at a median of 20 (IQR, 16-27) days after receipt of the additional vaccine. The frequency of local side effects was 65% (largely pain at the site of injection) and of systemic side effects was 50% (Fig 4). No patient experienced any severe adverse or allergic reaction; side effects were self-reported as mild or moderate in all cases. Before receipt of the additional dose, the GMC was 1.05 log\textsubscript{10} U/mL; 11 individuals had negative antibody titers. Antibody concentrations rose in 30 of 32 individuals, but two participants (both patients with chronic lymphocytic leukemia treated with obinutuzumab in the prior year) remained seronegative (Fig 4). The GMC after vaccination was 3.17 log\textsubscript{10} U/mL, comparable with baseline immunogenicity among healthy (noncancer) recipients of mRNA-1273 or BNT162b2 without prior infection. In an exploratory analysis, the degree of titer increase appeared to vary according to initial vaccine, additional dose, and whether the additional dose was homologous to the initial vaccine (Data Supplement). Neutralization titers rose similarly in the subset of patients with available measures (Data Supplement).

**DISCUSSION**

We studied the immunogenicity and reactogenicity of SARS-CoV-2 vaccines in a large, prospective cohort of patients with diverse solid-organ and hematologic malignancies. By assessing both binding antibodies and antibody neutralization, we found that responses to the three vaccines deployed under EAU in the United States are impaired modestly in patients with cancer relative to healthy controls, and vary according to vaccine, age, cancer type, and therapy. The frequency of local or systemic reactions in patients with cancer was similar to rates reported in healthy individuals, and systemic symptoms were more common in patients with prior infection. Systemic reactogenicity was associated with the magnitude of immune response. Furthermore, additional doses of vaccine among patients with low responses had a favorable side-effect profile and induced immune responses.

There are several noteworthy findings in this study. Consistent with what has been previously observed in healthy controls, Ad26.COV2.S induced low responses, and few patients had measurable neutralization. We found that patients receiving chemotherapy in the prior year or bone-marrow transplant recipients had lower immune responses, but the magnitude of these effects were small (smaller than that of the vaccine type for example) and most still had neutralization titers predicted to be protective. Interestingly, individuals receiving immune checkpoint blockade tended to have enhanced neutralization. Although widely hypothesized, this latter finding had not been previously reported, to our knowledge. We speculate that this may be because of enhanced CD4\textsuperscript{+} T-cell help leading to qualitatively improved B-cell activation, affinity maturation, and antibody production. Similarly, although widely hypothesized and assessed in small studies, the association between prior infection and reactogenicity, and between systemic reactogenicity and immunogenicity, has not been robustly assessed until now, yet is important for public health messaging.

These data have several salient clinical implications. Although the exact correlate of protection has not been determined, animal studies, randomized trials of prophylactic neutralizing antibodies, and correlative studies suggest that neutralizing antibody titer and binding antibody titers are a correlate of protection from infection or severe disease. First, these data reinforce public health messaging that SARS-CoV-2 vaccines are safe—even in an oncology patient population. Side effects to vaccines are mild or moderate and correlate with enhanced responses. Most individuals with cancer achieve responses that are likely to be sufficient to protect against severe disease. Second, given differences in immune responses based upon vaccine type (eg, 69% of patients who received Ad26.COV2.S had undetectable neutralization), our data suggest that where options exist, mRNA vaccines be prioritized for patients with cancer. Moreover, patients who received the Ad26.COV2.S vaccine should be considered for additional vaccine doses. The higher immunogenicity of mRNA1273 compared with BNT162b2 may plausibly be attributable to the higher administered
A dose of the former. Third, chemotherapy exposure appeared to have a long-lasting, albeit modest, impact on immunogenicity; larger studies may be required to understand whether holding chemotherapy around vaccination affects immunogenicity. Fourth, corticosteroids appeared to blunt binding antibody titers but did not significantly affect neutralization titers. Finally, additional booster vaccine doses appear well tolerated in patients with cancer, as has been observed in solid-organ transplant recipients, and are capable of inducing immune responses comparable with those achieved by healthy individuals after the primary vaccine series (in patients not on

**FIG 2.** Antispike immunoglobulin A/G/M antibody concentrations (top row) and neutralization titers following mRNA-1273 (left column), BNT-162b2 (middle column), or Ad26.COV2.S (right column) according to cancer-directed therapies received in the preceding 12 months among participants without prior infection (nucleocapsid antibody-negative). Horizontal line denotes the GMC or titer and whiskers denote the 95% CI. Corresponding adjusted statistical comparisons are provided in Table 2. GMC, geometric mean concentration; GMT, geometric mean titer; ICI, immune checkpoint blockade; pNT50, pseudovirus neutralization titer 50; TT, targeted therapy.

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FIG 3. Local (left column) and systemic (right column) reactogenicity of SARS-CoV-2 vaccines and their association with antispire immunoglobulin A/G/M antibody concentrations (middle row) or neutralization titer (bottom row). (A and B) Bars are colored according to vaccine (blue mRNA-1273, red BNT162b2, and teal Ad26.COV2.S) and timing of symptoms: lower solidly shaded box indicates after first dose only, middle moderately shaded box indicates after both doses, and upper lightly shaded box indicates after second dose only. (C-F) Horizontal line denotes the geometric mean concentration or titer and whiskers denote the 95% CI. pNT50, pseudovirus neutralization titer 50.
Collectively, these data suggest that antibody testing may help identify individuals who may be candidates for additional doses of vaccine.

This study has some important limitations. (1) Measures of immune response serve as a surrogate measure of protection, and the ultimate outcome of interest is whether patients develop breakthrough SARS-CoV-2 infection, and the severity thereof. (2) We assessed neutralization of the original Wuhan strain of SARS-CoV-2 but the beta, gamma, and delta viral variants show several-fold lower neutralization in other studies. (3) Although prospectively assessed, we cannot exclude unmeasured confounding explaining differences in immunogenicity between patient groups. (4) We report baseline vaccine response here; assessment of responses at additional timepoints will allow for more robust estimation of antibody decay rates. (5) We enrolled few patients receiving B-cell–depleting agents, in whom other studies have demonstrated low responses. (6) We did not assess T-cell responses whose role remains unclear in preventing infection. (7) The number of patients who received additional doses was small, thus limiting study of the correlates of response. Further studies to address these limitations are needed.

In summary, SARS-CoV-2 vaccines are well tolerated in patients with cancer, and most recipients achieve responses that are likely to be associated with protection. We define how receipt of specific vaccines or some therapies may impair responses. Studies on the effectiveness of vaccines in preventing breakthrough infection and the potential benefit of additional vaccine doses are required.
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