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Immunogenicity of SARS-CoV-2 vaccines in patients with breast cancer

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Abstract

Purpose: To explore the immunogenicity of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines in patients with breast cancer based on type of anticancer treatment.

Methods: Patients with breast cancer had anti-spike antibody concentrations measured ⩾14 days after receiving a full SARS-CoV-2 vaccination series. The primary endpoint was IgA/G/M anti-spike antibody concentration. Multiple regression analysis was used to analyze $\log_{10}$-transformed antibody titer concentrations.

Results: Between 29 April and 20 July 2021, 233 patients with breast cancer were enrolled, of whom 212 were eligible for the current analysis. Patients who received mRNA-1273 (Moderna) had the highest antibody concentrations [geometric mean concentration (GMC) in $\log_{10}$: 3.0 U/mL], compared to patients who received BNT162b2 (Pfizer) (GMC: 2.6 U/mL) (multiple regression adjusted $p = 0.013$) and Ad26.COV2.S (Johnson & Johnson/Janssen) (GMC: 2.6 U/mL) ($p = 0.071$). Patients receiving cytotoxic therapy had a significantly lower antibody titer GMC (2.5 U/mL) compared to patients on no therapy or endocrine therapy alone (3.0 U/mL) ($p = 0.005$). Patients on targeted therapies (GMC: 2.7 U/mL) also had a numerically lower GMC compared to patients not receiving therapy/on endocrine therapy alone, although this result was not significant ($p = 0.364$). Among patients who received an additional dose of vaccine ($n = 31$), 28 demonstrated an increased antibody response that ranged from 0.2 to >4.4 U/ mL.

Conclusion: Most patients with breast cancer generate detectable anti-spike antibodies following SARS-CoV-2 vaccination, though systemic treatments and vaccine type impact level of response. Further studies are needed to better understand the clinical implications of different antibody levels, the effectiveness of additional SARS-CoV-2 vaccine doses, and the risk of breakthrough infections among patients with breast cancer.

Keywords: breast cancer, CDK4/6 inhibitor, HER2+ breast cancer, hormone receptor-positive breast cancer, triple-negative breast cancer

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected over 250 million people and resulted in over 5 million deaths globally since December 2019.[1] As of August 2021, over 4 billion vaccine doses have been administered around the world.[1] Clinical trials with mRNA-1273 (Moderna), BNT162b2 (Pfizer), and Ad26.COV2.S (Johnson & Johnson/Janssen) have shown vaccines to be efficacious at preventing severe SARS-CoV-2 disease.[2–4] Testing for antibodies against SARS-CoV-2 nucleocapsid and spike proteins can provide evidence of prior infection and/or evaluate response to vaccination,

respectively.[5] Data suggest that antibody and neutralization titers correlate with protection against infection.[6]

Patients with cancer are disproportionally affected by SARS-CoV-2 as they have been found to have a higher risk of infection, severe disease, and death, which is largely driven by older age and increased comorbidities.[7,8] Despite the elevated risk, initial clinical trials of SARS-CoV-2 vaccines did not include patients with cancer; thus, there were initially limited prospective data on the immunogenicity of SARS-CoV-2 vaccines in patients with cancer.[9] Recent studies show that patients with cancer can have impaired responses to SARS-CoV-2 vaccines, including lower seroconversion rates and antibody concentration.[10–17] However, previous studies have not extensively analyzed the results based on anticancer treatment subtype in breast cancer. Chemotherapy and targeted therapies used for breast cancer treatment, such as cyclin-dependent kinase 4/6 (CDK4/6) inhibitors, are known to have hematologic adverse effects such as neutropenia and lymphopenia.[16,17] Given the importance of these cells in modulating immune responses to vaccines, such adverse effects could potentially impact response to the SARS-CoV-2 vaccine. We have previously reported on the immunogenicity and reactogenicity of SARS-CoV-2 vaccines in adults with solid-organ or hematologic cancers as part of the Cancer, Covid and Vaccination (CANVAX) prospective cohort study.[18] Here, we report the immunogenicity of SARS-CoV-2 vaccines in patients with breast cancer, both overall and in subgroups receiving specific therapies, from the CANVAX study.

Methods

Study design, eligibility, and study procedures

CANVAX, a prospective cohort study, enrolled adults receiving care at the Massachusetts General Hospital Cancer Center who were eligible to receive or had received a SARS-CoV-2 vaccine.[18] It was pre-planned to further explore disease-specific cohorts. Participants were recruited by clinician referral and there was a specific effort within the breast cohort to recruit patients on CDK4/6 inhibitors. At the time of consent, a baseline questionnaire was administered either in person or electronically. Questions included those regarding demographic information, cancer history, SARS-CoV-2 exposure and infection, and vaccination status, including timing. Blood was collected for nucleocapsid and spike antibody testing $\geqslant$14 days after receiving a full vaccination series. Among participants who reported a receipt of an additional vaccination, anti-spike antibodies were tested again, regardless of timing relative to the initial series. Additional chart review was performed to obtain cancer history, complete blood counts, and therapies received within 1 year prior to enrollment.

The current analysis focuses on CANVAX participants diagnosed with breast cancer who completed the baseline survey and antibody testing between 21 April 2021 and 8 August 2021. Spike and nucleocapsid results from the primary timepoint were returned to participants. Patients with long-term immunosuppressant use or with autoimmune conditions were excluded in our analysis. This study was approved by the Mass General Brigham Human Research Committee (2021P000746).

Antibody assays

As previously reported in the CANVAX study,[18] blood was collected in serum separator tubes and sent to the Massachusetts General Hospital Core Clinical Laboratory, a Clinical Laboratory Improvement Amendments certified lab, for antibody testing using the Roche Elecsys Anti-SARS-CoV-2 assay (Roche Diagnostics, Indianapolis, IN, USA). Total anti-spike (IgA/M/G) antibody concentrations ranged from antibody binding index (cutoff index, COI) $<$0.4 U/mL to $>$2500 U/mL. Results $>$2500 U/mL triggered additional manual dilution (where sample availability allowed) to yield titers up to 250,000 U/mL. An antibody binding index (COI) $>$0.8 was considered positive while an antibody binding index (COI) $<$0.4 was considered negative. Participants who received a negative test result were offered additional testing 7–14 days later. Those with negative or anti-spike antibody titers $<$100 U/mL were referred at the discretion of the treating oncologist to clinical immunology specialists for further counseling on potential for an additional vaccine dose once Centers for Disease Control and Prevention (CDC) guidelines allowed. Measurable anti-nucleocapsid antibody on the Roche Elecsys Anti_SARS-CoV-2 total (nucleocapsid) assay suggested prior SARS-CoV-2 infection. All assays were run concurrently and blinded to clinical information.

Treatment group classification

We included treatment administered within one calendar year from the date of blood collection. Since this study was focused on understanding the immune response of patients with cancer, we grouped treatments based on their immunological effects into three categories – no therapy/endocrine therapy alone (including tamoxifen, aromatase inhibitors, fulvestrant, ovarian function suppression), targeted therapy, and cytotoxic therapy. Patients who had not received any therapy within the past year were grouped with patients who only received endocrine therapy (control group), since unlike chemotherapy and targeted therapies such as CDK4/6 inhibitors, endocrine therapies have less immunomodulatory effects. Patients receiving CDK4/6 inhibitors, phosphatidylinositol 3-kinase (PI3K) inhibitors, protein kinase B (AKT) inhibitors, and poly (ADP-ribose) polymerase (PARP) inhibitors were grouped together under the category of targeted therapies. Given the potential myelosuppressive effects, patients receiving antibody drug conjugates (ADC) were grouped together with chemotherapy in the cytotoxic therapy group. Immune checkpoint inhibitors (ICI) were also included in this group, because unlike many other malignancies, ICI in breast cancer is at least initially combined with chemotherapy and all patients within this group received chemotherapy within the prior year. Patients with human epidermal growth factor receptor 2-positive (HER2+) breast cancer on anti HER2 antibody therapy alone were included with the cytotoxic therapy group if they also received chemotherapy within the prior year or with the no therapy group if they had not. If a patient had multiple treatment types within the past year, they were categorized based on the following order: cytotoxic therapy, targeted therapy, and no therapy/endocrine therapy alone. For example, if a patient had received both chemotherapy and a CDK4/6 inhibitor within the past year, the patient was categorized into the cytotoxic therapy group. Sensitivity analyses were performed regarding timing of therapies relative to vaccination.

Statistical analysis

Additional patient characteristic and clinical information were extracted during chart review. Data analyses were performed in R (v4.1.2) using the *lm()* and *glm(family=binomial)* functions. The primary endpoint used in this study was IgA/G/M anti-spike antibody concentration. We modeled $\log_{10}$-transformed antibody concentration as the dependent variable, and age, vaccine group, receptor status, therapy type, prior infection, and weeks post-vaccination as the independent variables. All p values reported are adjusted (i.e. multiple regression). Since patients with an antibody titer concentration below 100 U/mL were referred for counseling on additional vaccine doses, we also compared frequencies of patients with antibody titers below 100 U/mL between the different treatment groups using chi-square and Fisher's exact test. p values below 0.05 were considered significant. Figures were created using GraphPad Prism.

Results

Patient characteristics

Between 21 April 2021 and 8 August 2021, 233 patients with breast cancer were enrolled and 212 were eligible for the current analysis (Figure 1). Patient demographics, cancer characteristics, treatment history, and vaccine received are summarized in Table 1. The median age of study participants was 58.6 (range: 27.7–93.7). Of note, most patients had stage IV disease, invasive ductal carcinoma, and intermediate or high-grade cancer. The most common receptor status was hormone receptor-positive (HR+)/human epidermal growth factor-2 negative (HER2−). Most patients (50.5%) received their initial vaccination series with BNT162b2 (two doses), 35.8% with mRNA1372 (two doses), and 13.7% with Ad26.COV2.S (single dose). The median time between final dose of vaccination and antibody sampling was 70 days [interquartile range (IQR): 41.25–97.75 days] for patients who received the BNT162b2 vaccine, 82 days (IQR: 43–103 days) for patients who received the mRNA1372 vaccine, and 84.5 days (IQR: 64.75–113.5 days) for patients who received the Ad26.COV2.S vaccine. Nine patients (4.2%) reported having a prior SARS-CoV-2 infection. Across the study cohort, 66 patients received chemotherapy within 1 year of SARS-CoV-2 vaccination. Of those 66 patients, 10 received ICI concurrently and 15 received an ADC (Supplemental Figure 1). In all, 64 patients received a CDK4/6 inhibitor, and among these 64 patients, 48 (75.0%) received palbociclib, 9 (14.1%) received ribociclib, and 7 (10.9%) received abemaciclib. In all, 31 patients received endocrine therapy alone and 45 patients received no therapy within the past year. The median number of months (range) on current or most

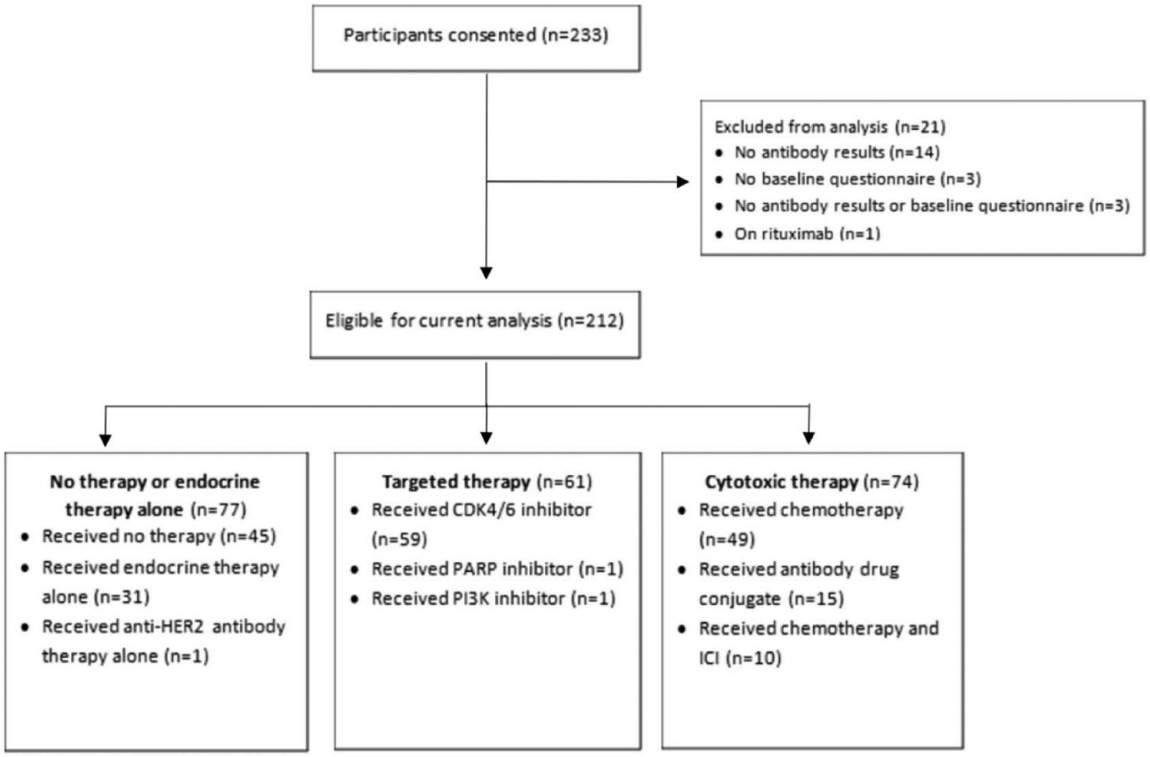

Figure 1. Patient disposition diagram.

recently completed treatment was 2.5 (0.2–116.7) for chemotherapy, 2.8 (0.5–18.4) for ICI, 25.9 (1.0–176.9) for endocrine therapy alone, and 12.0 (0.4–67.5) for other targeted therapies. For patients with metastatic breast cancer, the median number of prior lines of therapy was 1.

Prevalence of antibody-confirmed prior SARS-CoV-2 infection

Anti-nucleocapsid proteins were positive in 11 patients (5.2%). Among these 11 patients, only six (54.5%) reported a known history of SARS-CoV-2 infection. Three patients (1.4%) reported having a prior SARS-CoV-2 infection but had undetectable nucleocapsid antibodies.

Immunogenicity of SARS-CoV-2 vaccines

We performed a multiple-variable regression model with $\log_{10}$-transformed antibody titer concentration as the dependent variable, and age, vaccine, receptor status, therapy, prior infection, and time from vaccination to sampling as the independent correlates. The results are presented in Table 2. These correlates are explored in the following sections.

Vaccine type and prior infection. We first analyzed anti-spike titers of patients based on vaccine received. Patients who received the mRNA-1273 vaccine had the highest antibody concentrations (geometric mean concentration (GMC) in $\log_{10}$ U/mL: 3.0), which was higher than the patients who received the BNT162b2 vaccine (GMC: 2.6) (multiple regression adjusted $p = 0.013$; Table 2). The GMC difference between patients who received mRNA-1273 and Ad26.COV2.S (GMC: 2.6) was also numerically large, but not statistically significant, with a notably smaller sample of patients receiving Ad26.COV2.S.

Prior SARS-CoV-2 infection was associated with significantly higher antibody titers [0.863 $\log_{10}$ U/mL; 95% confidence interval (CI), 0.289, 1.438, $p = 0.004$; Table 2]. This aligns with what was observed in the larger CANVAX cohort as well as what has been observed in non-cancer patients.[19–21]

Age and time of sampling. Increasing age was associated with lower antibody concentrations ($p < 0.001$, Table 2). There was no association between antibody titers and timing of sampling from first vaccine dose.

Table 1. Patient characteristics.

Median age (range), y	**58.6 (27.7–93.7)**
	***N* (%)**
Gender	
Female	210 (99.1)
Male	2 (0.9)
Stage	
I	54 (25.8)
II	48 (22.5)
III	13 (6.1)
IV	77 (36.2)
Unknown	20 (9.4)
Tumor histology	
Invasive ductal carcinoma	165 (77.5)
Ductal carcinoma *in situ* alone	6 (2.8)
Invasive lobular carcinoma	14 (6.6)
Mixed invasive ductal/lobular carcinoma	25 (12.2)
Other	2 (0.9)
Grade	
1	10 (4.7)
2	94 (44.3)
3	102 (48.1)
Unknown	6 (2.8)
Receptor status	
HR+/HER2–	146 (68.9)
HR-/HER2+	5 (2.4)
HR+/HER2+	26 (12.3)
TNBC	35 (16.5)
Vaccine received	
BNT162b2	108 (50.5)
mRNA-1273	75 (35.8)
Ad26.COV2.S	29 (13.7)
Prior infection (reported)	
Yes	9 (4.2)
No	203 (95.8)
Chemotherapy	
Yes	66 (31.1)
No	146 (68.9)
ICI	
Yes	9 (4.2)
No	203 (95.8)
CDK4/6 inhibitor	
Palbociclib	48 (22.6)
Ribociclib	9 (4.2)
ABEMaCICLIB	7 (3.3)
No CDK4/6 inhibitor	148 (69.8)
Prior surgery	
Yes	181 (85.4)
No	31 (14.6)
Prior radiation	
Yes	113 (53.3)
No	99 (46.7)

CDK4/6, cyclin-dependent kinase 4/6; HER2+, human epidermal growth factor receptor 2-positive; HER2–, human epidermal growth factor-2 negative; HR, hormone receptor; ICI, immune checkpoint inhibitor; TNBC, triple-negative breast cancer.

Response based on therapy type. The GMCs in $\log_{10}$ U/mL along with a 95% CI for each treatment group are shown in Figure 2. Compared to patients receiving no therapy or endocrine therapy alone (GMC: 3.0), patients receiving cytotoxic therapy (GMC: 2.5) within the preceding 12 months had significantly lower antibody concentrations, after adjusting for age, vaccine, time from vaccination to sampling, receptor status, and prior infection ($p = 0.005$; Figure 2; Table 2). Patients receiving targeted therapies (GMC: 2.7) also had a lower antibody concentration than patients receiving no therapy or endocrine

Table 2. Multiple regression model with anti-spike IgA/G/M antibody concentration as the response variable and age, vaccine, prior infection, receptor status, treatment modality, and time (in weeks) from first dose to antibody sampling as the independent variables.

	Effect size (log_{10} U/mL)	95% CI	Adjusted *p* value
Age (per 1 year)	−0.17	−0.028, −0.007	<0.001
Vaccine			
mRNA-1273	Ref.		
BNT162b2	−0.362	−0.645, −0.078	0.013
Ad26.COV2.S	−0.386	−0.805, 0.033	0.071
Prior infection (serology)			
Negative	Ref.		
Positive	0.863	0.289, 1.438	0.004
Receptor status			
HR+/HER2−	Ref.		
HR-/HER2+	−0.504	−1.372, 0.364	0.254
HR+/HER2+	0.350	−0.084, 0.784	0.113
HR-/HER2−	−0.482	−0.882, −0.083	0.018
Treatment			
No therapy/endocrine alone	Ref.		
Targeted therapy	−0.160	−0.506, 0.186	0.364
Cytotoxic therapy	−0.480	−0.809, −0.151	0.005
Time (per week after 1st dose)	0.012	−0.013, 0.036	0.344

CI, confidence interval; HER2+, human epidermal growth factor receptor 2-positive; HER2−, human epidermal growth factor-2 negative.

therapy alone, although this result did not reach significance.

In addition, we compared the frequency of patients who had an antibody titer below 100 U/mL between the three treatment groups. Among the patients in the no therapy/endocrine therapy alone group, 9.1% (7/77) had antibody titers below 100 U/mL while 16.4% (10/61) and 21.6% (16/74) of patients in the targeted therapy and cytotoxic therapy groups, respectively, had antibody titers below the 100 U/mL mark ($p = 0.103$).

A sub-analysis focused on endocrine therapy alone *versus* CDK4/6 inhibitors is presented in Figure 3. We conducted another multiple regression analysis looking at differences between treatment with endocrine therapy alone and CDK4/6 inhibitor therapy (with or without endocrine therapy) (Table 3). The antibody titer GMC in log_{10} for patients on endocrine therapy alone was 3.0 U/mL, which was numerically higher than the antibody titer GMC for patients on CDK4/6 inhibitors (GMC: 2.8 U/mL). However, this difference was not significant, after adjusting for other factors (multiple regression adjusted $p = 0.814$). In addition, we compared the frequency of patients who had an antibody titer below 100 U/mL between the two treatment groups. Of note, only one patient (3.2%) in the endocrine therapy alone group had an antibody titer value below 100 U/mL while 10 patients (16.9%) in the CDK4/6 inhibitor group had an antibody titer below 100 U/mL ($p = 0.089$). While

patients in the CDK4/6 inhibitor group appear to have lower antibody titers, our results did not reach significance. This is likely because of our limited sample size for these two treatment groups. Power analysis for multiple regression demonstrates that for a sample size of 90 patients, our power level is 0.64.

Response based on timing of chemotherapy. Because some patients in our cohort completed chemotherapy several months prior to the sampling date, we performed a sensitivity analysis in which patients who had not received chemotherapy within 3 months of their sampling date were removed from the cytotoxic therapy group. These patients were moved into the no therapy/endocrine therapy alone group or targeted therapy group, depending on their current treatment status. The results of this multiple regression analysis are presented in Supplemental Table 2 with GMCs in $\log_{10}$ presented in Supplemental Figure 1. The analysis demonstrates that there is no change in the significance of our results.

Response based on disease characteristics. Receptor status was also included in our multiple regression analysis. Patients with triple-negative breast cancer had the lowest antibody titer GMC in $\log_{10}$ (GMC: 2.4 U/mL), which was significantly lower than patients with HR+/HER2− breast cancer (GMC: 2.8 U/mL), after controlling for other correlates (Table 2, multivariate adjusted $p = 0.021$). There was no significant difference in antibody concentrations between patients with and without metastatic cancer ($p = 0.398$, respectively).

Responses to additional SARS-CoV-2 vaccines

In all, 31 participants reported receiving an additional dose of vaccine. The median number of days between primary vaccination series and the additional vaccine was 171 days (IQR: 113.5–197.5 days). The median number of days between booster and antibody sampling was 35 days (IQR: 29.5–56 days). The antibody titers in these patients before and after the additional dose are shown in Figure 4. Of those 31 patients, 2 (6.5%) had first received the Ad26.COV2.S vaccine, 10 (32.3%) had received the mRNA-12 vaccine, and 19 (61.3%) had received the BNT162b2 vaccine. All patients received an additional dose of mRNA-1273 ($n = 14$, 45.2%), BNT162b2 ($n = 16$, 51.6%), or Ad26.COV2.S ($n = 1$, 3.2%) vaccines. Prior to additional doses of vaccination, the GMC in $\log_{10}$ was 2.5 U/mL. After receipt of additional vaccine doses, the GMC in $\log_{10}$ was 3.5 U/mL. Three patients showed a lower antibody response after the additional dose, and all other patients showed a higher antibody response that ranged from GMC $\log_{10}$ 0.2 U/mL to >4.4 U/mL.

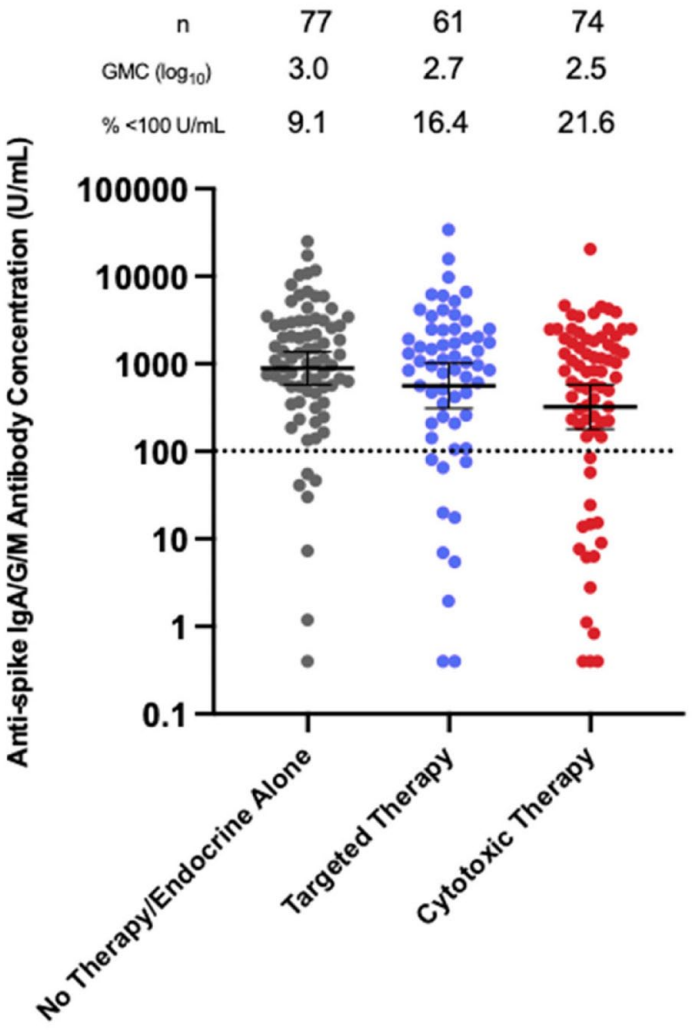

Figure 2. Anti-spike IgA/G/M antibody concentration (U/mL) based on treatment group. Horizontal line denotes the GMC and whiskers denote the 95% CI. Dotted line corresponds to 100 U/mL cutoff. Number of patients in each treatment group, GMC in $\log_{10}$ U/mL, and percentage of individuals with antibody titers below 100 U/mL are shown above each group. Corresponding statistical components are presented in Table 2.
CI, confidence interval; GMC, geometric mean concentration.

Discussion

Previous studies have focused on understanding the response to SARS-CoV-2 vaccines in patients with cancer broadly or in specific subsets of patients with breast cancer.[7,11,22,23] To

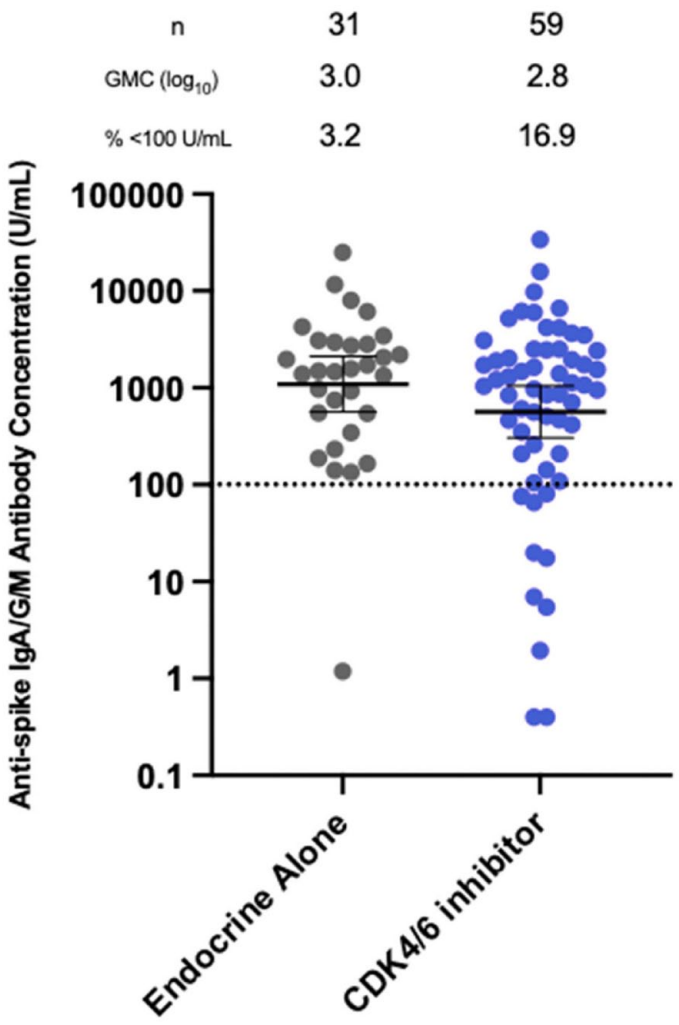

Figure 3. Comparison of anti-spike IgA/G/M antibody concentration (U/mL) between patients on endocrine therapy alone and patients on CDK4/6 inhibitors (with or without endocrine therapy). Horizontal line denotes the GMC and whiskers denote the 95% CI. Dotted line corresponds to 100 U/mL cutoff. Number of patients in each treatment group, GMC in $\log_{10}$ U/mL, and percentage of individuals with antibody titers below 100 U/mL are shown above each group. Corresponding statistical components are presented in Table 3.
CDK4/6, cyclin-dependent kinase 4/6; CI, confidence interval; GMC, geometric mean concentration.

our knowledge, studies have yet to perform a comprehensive analysis on patients with breast cancer who received a SARS-CoV-2 vaccine. In this study, we sought to understand the immunological response to SARS-CoV-2 vaccines specifically among patients with breast cancer and to understand how different breast cancer treatments may impact this immune response. To accomplish these aims, we measured antibody titers, which have been shown to be strong predictors of protection from severe disease.[24]

Similar to the full CANVAX population, we found that patients with breast cancer receiving the mRNA-1273 vaccine had the highest antibody titers.[18] We also found that compared to patients not on therapy/endocrine therapy alone, patients on chemotherapy (including ADCs or ICI) within the prior year had significantly lower antibody titers. Unlike in many other malignancies, ICI in breast cancer is at least initially combined with chemotherapy and therefore these treatment categories were combined. Patients on targeted therapies that have known immunosuppressive effects such as CDK4/6 inhibitors, AKT inhibitors, PI3K inhibitors, and PARP inhibitors within the prior year had a lower antibody titer compared to patients not on therapy/endocrine therapy alone, although this difference did not reach significance possibly due to limited sample size. A subset analysis further explored differences in immunogenicity between patients on CDK4/6 inhibitors (with or without endocrine therapy) and patients only on endocrine therapy. While our results did not reach significance again likely due to sample size, we did find that when patients on CDK4/6 inhibitors had numerically lower antibody titers and that a higher percentage of patients on CDK4/6 inhibitors had antibody titers that fell below the 100 U/mL mark. When comparing patients on no therapy/endocrine therapy alone to patients on all other treatments (chemotherapy, ADC, ICI, targeted therapy), we found that the latter group of patients had significantly lower antibody titers.

While both chemotherapies and targeted therapies such as CDK4/6 inhibitors are known to have immunosuppressive effects, it is noteworthy that only patients in the cytotoxic therapy group had significantly lower antibody titers when compared to patients not on therapy/endocrine therapy alone. This finding may, in part, also be due to the nature of the immunosuppressive effects of each treatment. CDK4/6 inhibitors are cytostatic while chemotherapies are cytotoxic, meaning that the immunosuppressive effects of CDK4/6 inhibitors are reversible while those of chemotherapies take a significantly longer time to reverse.[25] Patients receiving chemotherapy are also more likely to be on steroids, which may also affect response.

Among a growing literature on cancer treatment during the SARS-CoV-2 pandemic, our results begin to clarify the effects of breast cancer treatment on SARS-CoV-2 vaccine immune responses. Patients on chemotherapy within the prior year

Table 3. Multiple regression model with anti-spike IgA/G/M antibody concentration as the response variable and age, vaccine, prior infection, receptor status, treatment modality (CDK4/6 inhibitor *versus* endocrine therapy alone), and time (in weeks) from first dose to antibody sampling as the independent variables.

	Effect size (log_{10} U/mL)	95% CI	Adjusted *p* value
Age (per 1 year)	−0.03	−0.041, −0.014	<0.001
Vaccine			
mRNA-1273	Ref.		
BNT162b2	0.028	−0.376, 0.432	0.891
Ad26.COV2.S	0.246	−0.373, 0.865	0.439
Prior infection (serology)			
Negative	Ref.		
Positive	1.034	0.323, 1.745	0.006
Receptor status			
HR+/HER2−	Ref.		
HR-/HER2+		N/A	
HR+/HER2+	0.274	−0.516, 1.064	0.499
HR-/HER2−	−1.001	−2.747, 0.745	0.265
Treatment			
Endocrine alone	Ref.		
CDK4/6 inhibitor	−0.050	−0.467,0.366	0.814
Time (per week after 1st dose)	−0.031	−0.065, 0.003	0.072

CDK4/6, cyclin-dependent kinase 4/6; CI, confidence interval; HER2+, human epidermal growth factor receptor 2-positive; HER2−, human epidermal growth factor-2 negative.

appear to have lower immune responses compared to patients with breast cancer receiving other treatments. Many patients whose antibody titers demonstrated impaired immune response were referred to clinical immunology specialists, at the discretion of the treating oncologist, for further counseling on the potential for an additional vaccine dose. The majority of those who received an additional vaccination showed a higher antibody concentration than they had after completion of their initial vaccine series. While the CDC currently recommends that everyone who is eligible should receive a booster dose at least 6 months after their initial vaccine series, these findings demonstrate the potential for using antibody testing to identify patients who could benefit from additional booster vaccine doses outside of the current guidelines to augment their protection against SARS-CoV-2.[26]

Both the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) suggest a benefit in receiving a third dose of the SARS-CoV-2 vaccines, but state that each patient has individual risks and benefits and should thus discuss with their physician before receiving booster doses.[27,28] Antibody testing could potentially be incorporated into these discussions to help guide physicians on which patients should receive booster doses.

Another point of contention within breast cancer literature is the use of CDK4/6 inhibitors during the SARS-CoV-2 pandemic. Some studies have suggested that CDK4/6 inhibitor treatment could impair patients' immune responses,[29,30] while others have suggested that CDK4/6 inhibitor use is safe during the pandemic.[31,32] Recently, Zagouri

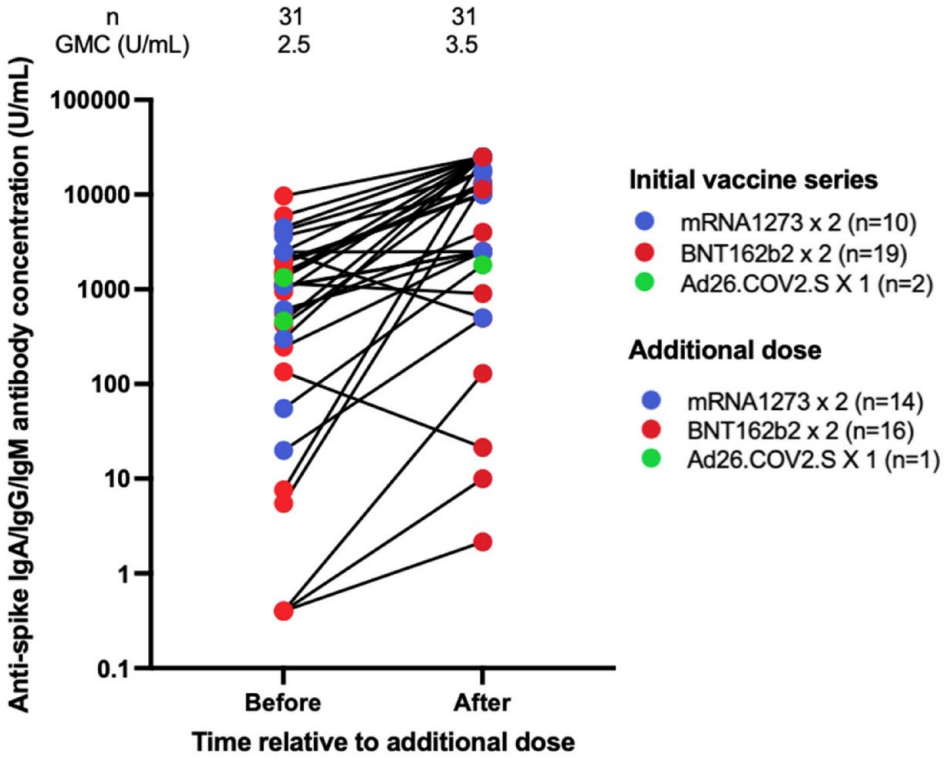

Figure 4. Comparison of anti-spike IgA/G/M antibody concentration (U/mL) prior to and after additional doses of SARS-CoV-2 vaccines following completion of the primary vaccine series ($n = 33$). Each point set connected by a line indicates one patient's antibody levels before and after receipt of an additional dose of vaccine. The color of each point indicates which vaccine was received (refer to legend).
SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

and colleagues conducted a study of 21 patients with breast cancer on CDK4/6 inhibitors and demonstrated that these patients had a similar immune response as healthy controls.[33] In our study, we obtained similar results with an expanded patient cohort ($N = 64$). This suggests that treatment with CDK4/6 inhibitors during the pandemic is likely safe. However, given our limited sample size, further studies with a larger sample size would be needed to confirm this finding.

Our study has several limitations. We did not evaluate time of systemic therapy in relationship to timing of the vaccine and treatment groups are broadly characterized based on therapy within the prior year. Factors, such as timing of vaccine in relationship to administration of cytotoxic chemotherapy, type of chemotherapy regimen used, and use of concurrent steroids with many chemotherapy regimens, should be explored in future research. In addition, while this is the largest study of vaccine response among patients with breast cancer to date, sample size likely limited the sub-analyses. Next, the antibody titers reported in this study are only representative of the first and single measure of immune response. We plan to obtain spike antibody levels in 3-month intervals over the course of a year in a subset of patients to better understand how immune responses change longitudinally. It is also important to note that there are limited data on correlation between antibody levels and risk of poor outcomes from SARS-COV-2 infection. This study did not evaluate incidence of infection among these patients, or disease outcomes, which will be important to address in future studies. We also did not evaluate safety or side effects of vaccines in this population. Finally, the number of participants that received an additional vaccine dose was small in the current analysis, and further evaluation of the impact of additional doses and boosters, as well as the timing of such interventions in relationship to breast cancer therapy is needed.

In summary, most patients with breast cancer can generate anti-spike antibodies following SARS-CoV-2 vaccination, though systemic treatments and type of vaccine received can impact the level of response. Further studies are necessary to better understand the long-term antibody levels, correlation between antibody levels and clinical outcomes, and the effectiveness of additional SARS-CoV-2 vaccine doses among patients with cancer.

Declarations

Ethics approval and consent to participate

Institutional review board approval for this study was obtained from the Mass General Brigham IRB. Written informed consent was obtained from all participants.

Consent for publication

Not applicable.

Author contribution(s)

Elyssa Denault: Data curation; Writing – original draft; Writing – review & editing.

Erika Nakajima: Formal analysis; Writing – original draft; Writing – review & editing.

Vivek Naranbhai: Conceptualization; Data curation; Writing – review & editing.

Jennifer A. Hutchinson: Investigation; Writing – review & editing.

Lindsey Mortensen: Investigation; Writing – review & editing.

Elizabeth Neihoff: Investigation; Writing – review & editing.

Caroline Barabell: Investigation; Writing – review & editing.

Amy Comander: Investigation; Writing – review & editing.

Dejan Juric: Investigation; Writing – review & editing.

Irene Kuter: Investigation; Writing – review & editing.

Theresa Mulvey: Investigation; Writing – review & editing.

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Aditya Bardia: Investigation; Supervision; Writing – review & editing.

Laura M. Spring: Investigation; Supervision; Writing – original draft; Writing – review & editing.

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Availability of data and materials

Requests can be made to the corresponding author.

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Supplemental material

Supplemental material for this article is available online.

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