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Immunogenicity of two doses of BNT162b2 and mRNA-1273 vaccines for solid cancer patients on treatment with or without a previous SARS-CoV-2 infection

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Abstract

Previous studies on the immunogenicity of SARS-CoV-2 mRNA vaccines showed a reduced seroconversion in cancer patients. The aim of our study is to evaluate the immunogenicity of two doses of mRNA vaccines in solid cancer patients with or without a previous exposure to the virus. This is a single-institution, prospective, nonrandomized study. Patients in active treatment and a control cohort of healthy people received two doses of BNT162b2 (Comirnaty, BioNTech/Pfizer, The United States) or mRNA-1273 (Spikevax, Moderna). Vaccine was administered before starting anticancer therapy or on the first day of the treatment cycle. SARS-CoV-2 antibody levels against S1, RBD (to evaluate vaccine response) and N proteins (to evaluate previous infection) were measured in plasma before the first dose and 30 days after the second one. From January to June 2021, 195 consecutive cancer patients and 20 healthy controls were enrolled. Thirty-one cancer patients had a previous exposure to SARS-CoV-2. Cancer patients previously exposed to the virus had significantly higher median levels of anti-S1 and anti-RBD IgG, compared to healthy controls ($P = .0349$) and to cancer patients without a previous infection ($P < .001$). Vaccine type (anti-S1: $P < .0001$; anti-RBD: $P = .0045$), comorbidities (anti-S1: $P = .0274$; anti-RBD: $P = .0048$) and the use of G-CSF (anti-S1: $P = .0151$) negatively affected the antibody response. Conversely, previous exposure to SARS-CoV-2 significantly enhanced the response to vaccination (anti-S1: $P < .0001$; anti-RBD: $P = .0026$). Vaccine immunogenicity in cancer patients with a previous

Abbreviations: CDK 4/6, cyclin-dependent kinase 4/6; CT, chemotherapy; G-CSF, granulocyte-colony stimulating factor; HT, hormone therapy; MFI, median fluorescence intensity; N, nucleocapsid; RBD, receptor-binding domain; S1, spike 1; TKI, tyrosine-kinase inhibitor.

Nicla La Verde and Agostino Riva are co-first authors on this work. Davide Dalu and Maciej S. Tarkowski are co-last authors on this work.

exposure to SARS-CoV-2 seems comparable to that of healthy subjects. On the other hand, clinical variables of immune frailty negatively affect humoral immune response to vaccination.

KEYWORDS
cancer patients, COVID-19, immunogenicity, mRNA, vaccines

What's new?

Although mRNA-based vaccines that protect against infection with SARS-CoV2, the causative virus of COVID-19, are highly immunogenic in healthy individuals, the extent to which they provoke immune responses in cancer patients is less certain. Here, the immunogenicity of two doses of either of two SARS-CoV2 mRNA vaccines was investigated in cancer patients with solid tumors. Patients previously exposed to SARS-CoV2 exhibited strong immune responses to vaccination, similar to responses in healthy controls. Responses were more muted among patients with no prior SARS-CoV2 exposure. Antibody responses to vaccination also were negatively impacted by comorbidities, use of G-CSF and vaccine type.

1 | INTRODUCTION

On 11 March 2020 the World Health Organization (WHO) declared the novel coronavirus disease 2019 (COVID-19) outbreak a global pandemic.[1]

Common to other coronaviruses,[2,3] severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) internalization into host cells is mediated by S glycoproteins projecting from the viral surface. The S1 subunit of S protein contains the receptor-binding domain (RBD) sequence that specifically binds angiotensin-converting enzyme 2 (ACE-2) on host cells to allow virus entry.[4] First case of the SARS-CoV-2 infections in Italy was reported in February 2020. Since then, their numbers raised dramatically, causing almost 50% excess of deaths from any causes in March 2020.[5] At the end of 2021, the COVID-19 pandemic had caused almost 257 million infections worldwide, resulting in 5.1 million deaths.[6] Individuals older than 65 years and with comorbidities had higher risk of mortality and morbidity, such as severe illness, hospitalization, intensive care admission or invasive ventilation. Several studies have already demonstrated the increased vulnerability of cancer patients to COVID-19 because of greater infection rate and incidence of complications compared to the healthy population.[7,8] Cancer patients on active antiblastic treatment had worse consequences of SARS-CoV-2 infection,[9,10] especially if they had received it shortly before SARS-CoV-2 infection.[7,11] Studies conducted in prevaccination era have identified age, gender and comorbidities as the main risk factors of mortality from COVID-19 disease in cancer patients.[12,13]

The Healthcare System has been rapidly readapted to face the pandemic in order to protect especially frail patients, with significant impact on daily routines and emotional well-being of both health care professional, patients and their caregivers.[14,15]

The COVID-19 mitigation measures, such as lock down, staying at home, using facemasks, hand hygiene, physical distancing, the increased ventilation of indoor spaces and restricting protocols for hospital access had been applied but were not able to slow down the spread of the infection.[16]

In that scenario, the protection by immunization was urgently needed. In an unprecedented way, fast track approved mRNA-based vaccines, BNT162b2 vaccine (Pfizer-BioNTech) and mRNA-1273 (Moderna), were introduced already 9 months after the declaration of the pandemic and given first to healthcare professionals and high-risk groups. BNT162b2 and mRNA-1273 vaccines contain nucleoside-modified mRNA encoding the viral spike (S) glycoprotein of SARS-CoV-2 and are injected under usual 2-dose regimen, given 3 or 4 weeks apart, respectively. Early studies reported high effectiveness of both vaccines for the prevention of symptomatic COVID-19, at 95% for BNT162b2 vaccine and 94% for mRNA-1273.[15,16] These data were confirmed in subsequent real-world vaccination campaigns,[18-20] although the efficacy was reduced 24-week after the first two doses.[21] Clinical trials on the efficacy and safety of the COVID-19 vaccine however did not include vulnerable populations, as cancer patients. Studies conducted in patients with solid tumor reported that immunogenicity of the BNT162b2 vaccine significantly increased only after a vaccine boost at day 21 after the first dose,[22] although with lower antibody serum levels than healthy controls[23,24] which tend to wane more rapidly.[25] Anticancer treatments or steroids in solid or hematologic malignancies seemed to negatively affect the response to vaccination,[26] with lower median levels of the anti-spike IgG up to 7 weeks after the first dose.[27]

Real-world studies are ongoing in order to answer many relevant open questions about the number of vaccine doses needed and their appropriate timing of administration during the course of cancer treatment, the efficacy of anticancer therapies and the immunogenicity of the different SARS-CoV-2 vaccine according to the type of malignancy. Other variables such as cancer site, use of steroids or granulocyte-colony stimulating factor (G-CSF) and comorbidities warrant ad-hoc investigations.

The aim of the present study is to evaluate the immune-serological response after two doses of SARS-CoV-2 mRNA-vaccine in cancer patients and in a cohort of healthy subjects.

2 | MATERIALS AND METHODS

2.1 | Study design

This is a single institution, prospective, non-randomized study conducted at the Luigi Sacco Hospital in Milan, Italy.

The primary objective of the study was to verify the capability of two doses of mRNA vaccine to induce immunological response in patients with solid tumors. The secondary objective was to explore the correlation between patient characteristics, disease type, anticancer treatment characteristics and the immunological response to vaccine.

The antibody response was evaluated according to anti-S1 IgG (Antibodies against S-subunit detectable in serum of vaccinated patients) and anti-RBD IgG (Antibodies against RBD revealed in patients vaccinated or exposed to SARS-CoV-2 virus) level. In addition, anti-N IgG was evaluated to identify a previous SARS-CoV-2 infection.

We assessed SARS-CoV-2 exposure before the first dose (T0) and 30 days after the second dose of vaccine (T1), by measuring

TABLE 1 Demographic and clinical characteristics of cancer patients

	Cancer patients		Overall
	Without a previous SARS-CoV-2 infection N = 165	With a previous SARS-CoV-2 infection N = 30	N = 195
Age at tumor diagnosis			
Mean (SD)	59.1 (11.4)	56.2 (13.8)	58.6 (11.8)
Median (Q1-Q3)	60.9 (50.8-67.2)	57.9 (44.9-67.3)	60.4 (49.8-67.3)
Min-max	24.0-78.6	32.2-78.4	24.0-78.6
Tumor site			
Breast	84 (50.9)	16 (53.3)	100 (51.3)
Gastroenteric	24 (14.5)	6 (20.0)	30 (15.4)
Lung	20 (12.1)	4 (13.3)	24 (12.3)
Genitourinary	14 (8.5)	1 (3.3)	15 (7.7)
Gynecological	16 (9.7)	1 (3.3)	17 (8.7)
Head and neck	2 (1.2)	0 (0.0)	2 (1.0)
Other	5 (3.0)	2 (6.7)	7 (3.6)
Tumor stage[a]			
Limited	57 (34.5)	5 (16.7)	62 (31.8)
Advanced	106 (64.2)	25 (83.3)	131 (67.2)
>1 line of cancer treatment	113 (68.5)	22 (73.3)	135 (69.2)
Patients on treatment	137 (83.0)	29 (96.7)	166 (85.1)
Neoadjuvant	8 (4.8)	0 (0.0)	8 (4.1)
Adjuvant	26 (15.8)	5 (16.7)	31 (15.9)
Metastatic	98 (59.4)	24 (80.0)	122 (62.6)
Maintenance	5 (3.0)	0 (0.0)	5 (2.6)
Patients out of treatment	28 (17.0)	1 (3.3)	29 (14.9)
Treatment schedule (n = 166)			
1w	17 (12.4)	1 (3.4)	18 (10.8)
2w	7 (5.1)	1 (3.4)	8 (4.8)
3w	64 (46.7)	16 (55.2)	80 (48.2)
4w	15 (10.9)	5 (17.2)	20 (12.0)
Daily	34 (24.8)	6 (20.7)	40 (24.1)
Comorbidity			
No	71 (43.0)	15 (50.0)	86 (44.1)
=1	56 (33.9)	9 (30.0)	65 (33.3)
>1	38 (23.0)	6 (20.0)	44 (22.6)
Steroids	76 (46.1)	12 (40.0)	88 (45.1)
G-CSF	14 (8.5)	1 (3.3)	15 (7.7)

Abbreviations: 1w, weekly; 2w, every 2 weeks; 3w, every 3 weeks; 4w, every 4 weeks; Q1-Q3, interquartile range.
[a]Not applicable for two patients.

anti-N and anti-RBD antibody titers. The humoral immune response to the vaccine was assessed by measuring anti-S1 and anti-RBD antibody titers at T0 and T1.

2.2 | Subjects and samples

One hundred ninety-five consecutive patients affected by solid malignancies, both in active treatment and in follow-up, eligible for anti-COVID-19 vaccination, who attended the Department of Oncology, were enrolled. A second cohort of healthy subjects >18 years, identified among healthcare workers, undergoing anti-COVID-19 vaccine during the same time period was considered as a control group. All enrolled subjects received two doses of BNT162b2 (Comirnaty, BioNTech/Pfizer, The United States) or mRNA-1273 (Spikevax, Moderna) vaccine, administered intramuscularly 21 (BNT162b2) and 28 (mRNA-1273) days apart, before starting anticancer therapy or on the first day of the treatment cycle. The type of vaccine was randomly assigned

TABLE 2 Vaccines and antibodies measurement

	Healthy subjects N = 20	Cancer patients		
		Without a previous SARS-CoV-2 infection N = 165	With a previous SARS-CoV-2 infection N = 30	Overall N = 195
Age at vaccine first dose				
Mean (SD)	34.0 (12.6)	63.3 (11.6)	60.1 (12.4)	62.8 (11.8)
Median (Q1-Q3)	28.5 (25.0-42.0)	64.5 (54.6-72.0)	61.4 (48.9-71.2)	64.1 (53.8-72.0)
Min-max	21.0-63.0	26.9-84.3	33.3-82.2	26.9-84.3
Female sex	11 (55.0)	116 (70.3)	22 (73.3)	138 (70.8)
Anti-SARS-CoV-2 vaccine[a]				
mRNA-1273	0 (0.0)	49 (29.9)	6 (20.0)	55 (28.4)
BNT162b2	20 (100.0)	115 (70.1)	24 (80.0)	139 (71.6)
Missing	0	1	0	1
Timing of vaccine in relation to anticancer treatments administration (n = 166)				
At first cycle	—	21 (15.3)	1 (3.4)	22 (13.3)
After first cycle	—	116 (84.7)	28 (96.6)	144 (86.7)
IgG anti-N1				
Negative both at T0 and T1	20 (100.0)	165 (100.0)	0 (0.0)	165 (84.6)
Negative at T0, positive at T1	0 (0.0)	0 (0.0)	5 (16.7)	5 (2.6)
Positive at T0, negative at T1	0 (0.0)	0 (0.0)	4 (13.3)	4 (2.1)
Positive both at T0 and T1	0 (0.0)	0 (0.0)	21 (70.0)	21 (10.8)
Subject groups				
Group 1	0 (0.0)	27 (16.4)	1 (3.3)	28 (14.4)
Group 2	0 (0.0)	54 (32.7)	11 (36.7)	65 (33.3)
Group 3	0 (0.0)	54 (32.7)	15 (50.0)	69 (35.4)
Group 4	0 (0.0)	21 (12.7)	3 (10.0)	24 (12.3)
Group 5	0 (0.0)	9 (5.5)	0 (0.0)	9 (4.6)
Healthy subjects	20 (100.0)	—	—	—

Note: Group 1: patients in complete remission after surgery, untreated or pretreated with adjuvant chemotherapy (CT) completed since at least 12 months. Adjuvant hormone therapy (HT) was allowed. Group 2: patients in active treatment with CT. Group 3: patients treated with biological therapy (immunotherapy, CDK4/6 inhibitors, TKI and monoclonal antibody). Group 4: patients in treatment with a combination of CT and biological treatment. Group 5: patients receiving only HT in metastatic setting. Abbreviations: Q1-Q3, interquartile range; T0, at first dose of the vaccine; T1, 30 days after second dose of vaccine.

[a]Missing in one patient.

according to the availability at the vaccination center. Venous blood samples were drawn on K2-EDTA anticoagulant tubes before the first dose (T0) and 30 days after the second one of the vaccines (T1). Obtained plasma aliquots were stored at −20°C until use.

Patients were categorized into five groups, according to the setting (neoadjuvant, adjuvant or metastatic) and to the type of treatment. In details, the Group 1 includes patients in complete remission after surgery, untreated or pretreated with adjuvant chemotherapy (CT) completed since at least 12 months (adjuvant hormone therapy [HT] was allowed). Patients in active treatment with CT or with biological therapy (immunotherapy, CDK4/6 inhibitors, TKI and monoclonal antibody) were included in Group 2 and Group 3, respectively; whereas patients in treatment with a combination of CT and biological treatment were included in Group 4. Lastly, the Group 5 included patients receiving only HT in metastatic setting.

Data on anticancer therapies, the use of steroids or G-CSF and the presence of comorbidities (cardiovascular, metabolic, pneumological and rheumatological) were collected.

2.3 | Serological parameters evaluation

IgG levels against S1, RBD and N proteins of SARS-CoV-2 were simultaneously measured in human plasma samples using the Luminex xMAP SARS-CoV-2 Multi-Antigen IgG kit (Luminex Corp., Austin, Texas), a fluorescence bead-based multiplex assay that has received FDA authorization under a EUA (US FDA 2020; Available at: https://www.fda.gov/media/140257/download). Assay 96-well plates were read on a MAGPIX automated plate reader and the data were analyzed using xMAP MULTI IgG CoV-2 Assay Software (Luminex Corp., Austin, Texas). According to the lot number of the kits used, manufacturer provided threshold values for N, S1 and RBD which were set to 700 median fluorescence intensity (MFI) for all three antigens and 300 for the background. The antibody levels were reported as qualitative (seroconversion defined as titers ≥700 MFI) and as an MFI value in three time points.

2.4 | Statistical analysis

The continuous variables were described using mean and SD, the median with the first (Q1) and third (Q3) quartiles and minimum and maximum values, whereas categorical variables were described using frequencies and percentages. To compare the distributions of categorical variables, the χ^2 test and the Fisher exact test, as appropriate, were performed. The Wilcoxon test and the Kruskal-Wallis test, as appropriate, were performed to compare the distributions of continuous variables. The univariable and multivariable linear regression models were used to investigate the prognostic and predictive role of demographic and clinical factors on the anti-S1 IgG and anti-RBD IgG titers (expressed on the logarithmic scale) in cancer patients. The results are provided as the exponential of the estimate and of the confidence interval at 95% (95% CI). Moreover, subgroup analyses were performed according to the previous SARS-CoV-2 infection and in case of a statistically significant interaction (at 10% significance level) between a factor and the vaccine type. Statistical significance was set at $P < .05$ for a bilateral test, unless otherwise stated. The analysis was carried out using the SAS software (Statistical Analysis System, SAS Institute, Version 9.4).

3 | RESULTS

3.1 | Characteristics of the studied subjects

From January to June 2021, 215 subjects who received COVID-19 vaccine were enrolled, including 195 consecutive cancer patients

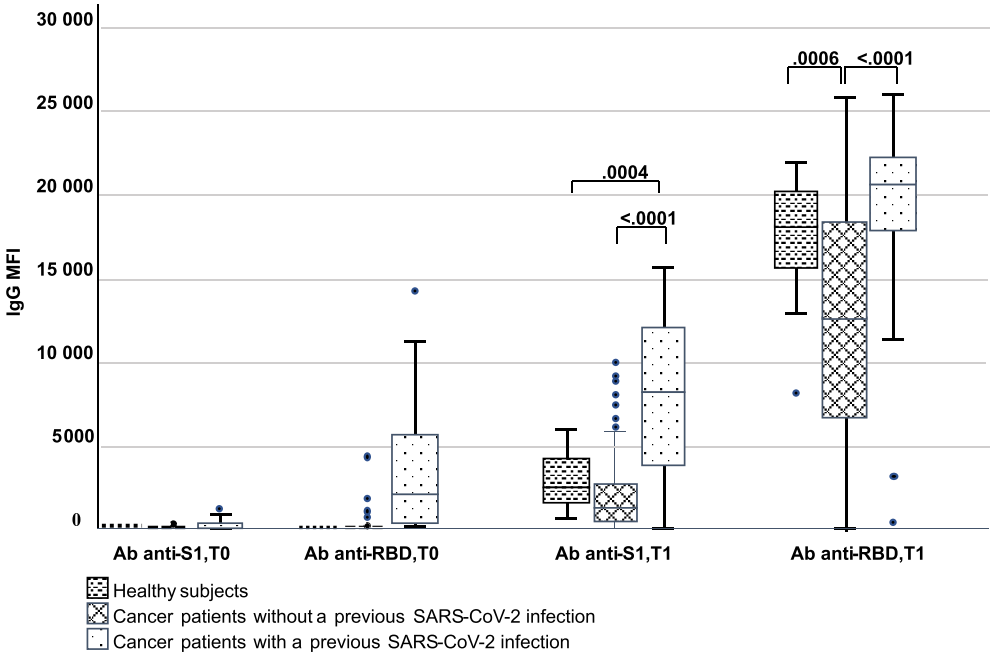

FIGURE 1 IgG anti-RBD and anti-S1 of SARS-CoV-2 in plasma of healthy vaccinated and cancer patients with or without a previous SARS-CoV-2 infection. MFI: median fluorescence intensity. T0: before the first dose of SARS-CoV-2 vaccine. T1: 30 days after the second dose of SARS-CoV-2 vaccine. Bars: interquartile range Horizontal lines inside bars: median values. Vertical lines and dots: minimum and maximum values. Numbers above the bars: *P* value for the interaction.

TABLE 3 Factors associated with IgG anti-RBD and anti-S1 SARS-CoV-2 vaccine response in cancer patients (univariable linear regression analysis)

	Anti-S1 antibody response			Anti-RBD antibody response		
Parameter	**Exp (intercept)**	**Exp (estimate [95% CI])**	***P*-value**	**Exp (intercept)**	**Exp (estimate [95% CI])**	***P*-value**
Cancer patients (vs healthy controls)	2604.04	0.48 [0.24-0.97]	**.0398**	17 299.45	0.53 [0.30-0.93]	**.0271**
Age at first dose (1 year increase)	3139.91	0.99 [0.97-1.00]	.1257	11 875.47	1.00 [0.98-1.01]	.5956
Female sex	1479.12	0.80 [0.49-1.29]	.3550	10 148.59	0.87 [0.58-1.29]	.4718
Active treatment	1307.71	0.96 [0.51-1.79]	.8902	9714.84	0.93 [0.56-1.56]	.7928
Group 2 (vs 1)	1307.70	0.70 [0.35-1.39]	.3024	9714.87	0.74 [0.42-1.30]	.2970
Group 3 (vs 1)		1.22 [0.61-2.40]	.5736		1.10 [0.63-1.92]	.7438
Group 4 (vs 1)		1.42 [0.61-3.30]	.4190		1.24 [0.62-2.49]	.5406
Group 5 (vs 1)		0.53 [0.17-1.70]	.2855		0.67 [0.26-1.76]	.4172
Post hoc contrasts						
Group 2 (vs 3)		0.57 [0.34-0.97]	**.0386**		0.68 [0.44-1.04]	.0747
Group 2 (vs 4)		0.49 [0.24-1.02]	.0561		0.60 [0.33-1.08]	.0901
Group 3 (vs 4)		0.86 [0.42-1.77]	.6767		0.88 [0.49-1.60]	.6823
Group 2 (vs 5)		1.31 [0.44-3.88]	.6199		1.10 [0.45-2.68]	.8329
Group 3 (vs 5)		2.29 [0.78-6.74]	.1316		1.63 [0.67-3.96]	.2788
Group 4 (vs 5)		2.67 [0.81-8.77]	.1055		1.84 [0.69-4.90]	.2190
Steroids	1540.07	0.64 [0.41-0.99]	**.0462**	10 707.93	0.71 [0.49-1.01]	.0588
G-CSF	1374.55	0.32 [0.14-0.72]	**.0062**	9526.09	0.60 [0.31-1.18]	.1381
BNT162b2 vaccine (vs mRNA-1273)	2216.14	0.46 [0.28-0.74]	**.0015**	13 408.71	0.59 [0.40-0.87]	**.0085**
One comorbidity (vs none)	1498.17	0.93 [0.57-1.54]	.7805	10 910.82	0.96 [0.64-1.44]	.8383
More than one comorbidity (vs none)		0.51 [0.29-0.90]	**.0209**		0.49 [0.31-0.77]	**.0023**
Presence of tumor[a]	960.37	1.48 [0.92-2.38]	.1053	8275.88	1.16 [0.78-1.71]	.4584
Timing of vaccine in relation to anticancer treatments administration: after first cycle (vs at first cycle)	782.30	1.69 [0.81-3.49]	.1583	8337.76	1.09 [0.61-1.95]	.7703
Previous line of therapy	1239.22	1.02 [0.63-1.65]	.9238	9014.86	1.02 [0.69-1.51]	.9064
Previous SARS-CoV-2 infection	974.52	5.29 [3.01-9.30]	**<.0001**	8230.73	2.01 [1.23-3.27]	**.0055**

Note: All the models, except the first, were performed including only cancer patients. Antibody titers were analyzed as on the logarithmic scale. Group 1: patients in complete remission after surgery, untreated or pretreated with adjuvant chemotherapy (CT) completed since at least 12 months. Adjuvant hormone therapy (HT) was allowed. Group 2: patients in active treatment with CT. Group 3: patients treated with biological therapy (immunotherapy, CDK4/6 inhibitors, TKI and monoclonal antibody). Group 4: patients in treatment with a combination of CT and biological treatment. Group 5: patients receiving only HT in metastatic setting. we used bold for the statistical significant *p*-value.
[a]Clinical or radiological evidence of disease.

and 20 healthy controls. Demographic and clinical characteristics of cancer patients are presented in Table 1. Among 195 cancer patients, 165 (84.6%) had never had an infection, 25 (12.8%) had a previous exposure to SARS-CoV-2 and 5 (2.6%) contracted it between T0 and T1. The median age at first vaccine dose of cancer patients was 64.1 years (Q1-Q3: 53.8-72.0) and 138 (70.8%) were women. Most of cancer patients received BNT162b2 vaccine (115 patients, 70.1% in nonexposed and 24 patients, 80% in exposed to SARS-CoV-2). Among 166 cancer patients on cancer treatment, the vaccine was injected when one or more cycle of therapy had already been administered in the vast majority (144 patients, 86.7%). All patients adhered to the schedule between the two doses, except for one patient who was quarantined for COVID-19. A tumor in advanced stage was observed in 131 patients (67.2%) and the breast cancer was the predominant tumor (100 patients, 51.3%). The majority of patients were receiving traditional chemotherapy (65 patients,33.3%) or targeted therapy alone (69 patients, 35.4%). In 45% of patients therapy was administered with a 3-week schedule. Only 44 cancer patients (22.6%) had more than one specific comorbid condition. Steroids and G-CSFs, at any dose and schedule, were administered to 88 (45.1%) and 15 cancer patients (7.7%), respectively. The median age of healthy volunteers was 28.5 years (Q1-Q3: 25.0-42.0), 11 (55.0%) were females and all were vaccinated with BNT162b2 vaccine. The

TABLE 4 Factors associated with IgG anti-RBD and anti-S1 SARS-CoV-2 vaccine response in cancer patients (multivariable linear regression analysis)

	Anti-S1 antibody response (N = 194)		Anti-RBD antibody response (N = 194)	
Parameter	**Exp (estimate [95% CI])**	***P*-value**	**Exp (estimate [95% CI])**	***P*-value**
Intercept	2793.55		13 947.35	
BNT162b2 vaccine (vs mRNA-1273)	0.39 [0.26-0.60]	**<.0001**	0.57 [0.39-0.84]	**.0045**
One comorbidity (vs none)	1.01 [0.65-1.58]	.9517	1.03 [0.70-1.53]	.8786
More than one comorbidity (vs none)	0.57 [0.34-0.94]	**.0274**	0.53 [0.34-0.82]	**.0048**
Previous SARS-CoV-2 infection	5.41 [3.15-9.28]	**<.0001**	2.08 [1.30-3.34]	**.0026**
Steroids	0.67 [0.37-1.20]	.1799		
G-CSF	0.38 [0.18-0.83]	**.0151**		
Group 2 (vs 1)	0.93 [0.43-2.05]	.8614		
Group 3 (vs 1)	0.91 [0.50-1.67]	.7685		
Group 4 (vs 1)	1.59 [0.66-3.83]	.2968		
Group 5 (vs 1)	0.83 [0.30-2.35]	.7309		
Post hoc contrasts				
Group 2 (vs 3)	1.02 [0.54-1.93]	.9490		
Group 2 (vs 4)	0.59 [0.31-1.12]	.1048		
Group 3 (vs 4)	0.57 [0.27-1.22]	.1475		
Group 2 (vs 5)	1.12 [0.40-3.09]	.8295		
Group 3 (vs 5)	1.09 [0.42-2.87]	.8535		
Group 4 (vs 5)	1.91 [0.64-5.70]	.2455		

Note: Antibody titers were analyzed as on the logarithmic scale. Multivariable models include variables statistically significant at univariable analysis. The area in gray indicates variables included in the model for anti-S1 and not in the model for anti-RBD. Group 1: patients in complete remission after surgery, untreated or pretreated with adjuvant chemotherapy (CT) completed since at least 12 months. Adjuvant hormone therapy (HT) was allowed. Group 2: patients in active treatment with CT. Group 3: patients treated with biological therapy (immunotherapy, CDK4/6 inhibitors, TKI and monoclonal antibody). Group 4: patients in treatment with a combination of CT and biological treatment. Group 5: patients receiving only HT in metastatic setting. we used bold for the statistical significant *p*-value.

demographic and clinical characteristics of cancer patients divided into groups defined according to the setting and the treatment type are presented in Table S1.

3.2 | Vaccine-induced humoral immune response: anti-RBD and anti-S1 SARS-COV-2 IgG levels and seroconversion rate

Vaccines and antibodies measurement are described in Table 2. The seroconversion rate (defined as titers ≥700 MFI) of cancer patients with previous exposure to SARS-CoV-2 (93.3%) was similar to the healthy individuals (95.0%, $P = 1.000$), as expected. The rate of seroconversion in patients without previous SARS-CoV-2 infection (66.7%) was significantly lower than that observed in healthy controls ($P = .0085$) and in patients with a previous SARS-CoV-2 infection ($P = .0020$). The vaccines and antibodies measurement in the different groups defined according to the setting and the treatment type are presented in Table S2.

MFI values for anti-RBD and anti-S1 IgG levels in the three groups are described in Figure 1. Cancer patients without previous exposure to the virus compared to healthy control group had statistically lower median levels of both anti-S1 (1322.0, Q1-Q3: 473.0-2733.0 vs 2590.0, Q1-Q3: 1731.8-4253.0, $P = .0013$) and anti-RBD IgG plasma levels (12 541.5, Q1-Q3: 6597.0-18 176.0 vs 18 088.8, Q1-Q3: 15 661.3-20 097.5, $P = .0006$).

In contrast, cancer patients previously exposed to the virus had statistically significantly higher median levels of both anti-S1 (8279.8, Q1-Q3: 4288.0-11 936.0) and anti-RBD IgG (20 732.5, Q1-Q3: 18 123.5-22 194.0), compared to healthy controls (anti-S1: $P = .0004$; anti-RBD: $P = .0349$) and to cancer patients without previous exposure to SARS-CoV-2 (both $P < .0001$). The comparison in terms of MFI values for anti-RBD and anti-S1 IgG levels among the groups defined according to the setting and the treatment type are presented in Table S3.

3.3 | Factors associated with IgG anti-RBD and anti-S1 SARS-CoV-2 vaccine response in cancer patients

Univariable and multivariable analyses of the factors potentially affecting the anti-RBD and anti-S1 IgG levels in cancer patients are presented in Tables 3 and 4, respectively.

No statistically associations were found between the levels of both antibodies and age, gender, timing of vaccination and use of steroids. Moreover, no statistically differences were found in terms of antibody levels between patients according to the group defined in the method section based on the antiblastic treatment (chemotherapy, targeted therapy, hormonal therapy or their combination) and the line of treatment administered.

At the univariable analysis, lower anti-S1 and anti-RBD IgG levels at T1 were detected for patients with more than one comorbidity compared to patients without any comorbidity and in patients who received BNT162b2 vaccine, whereas a previous exposure to SARS-CoV-2 significantly correlated to a higher antibody response. Moreover, statistically significant lower anti-S1 IgG levels were found for patients treated with chemotherapy compared to those treated with target therapy and for patients assuming steroids or G-CSF.

The multivariable analysis confirmed the negative correlation between anti-SARS-CoV-2 IgG levels and comorbidities (anti-S1: $P = .0274$; anti-RBD: $P = .0048$) and BNT162b2 vaccine (anti-S1: $P < .0001$; anti-RBD: $P = .0045$). The previous exposure to SARS-CoV-2 correlated with higher levels of both antigen specific IgGs (anti-S1: $P < .0001$; anti-RBD: $P = .0026$).

Lastly, patients assuming G-CSF had statistically significant lower levels of anti-S1 IgG ($P = .0151$). The results of the subgroup analyses on the anti-S1 IgG levels at T1 according to the G-CSF assumption and to the previous exposure to the SARS-CoV-2 virus are reported in Tables S4 and S5, respectively. A quantitative interaction between vaccine type and G-CSF was observed (P-value $= .0652$), identifying a worse impact of BNT162b2 vaccine on anti-S1 IgG level in patients receiving G-CSF, even if this association was not statistically significant due to the low number of patients. The subgroup analysis according to previous SARS-CoV-2 infection, confirmed a negative impact of BNT162b2 vaccine on anti-S1 IgG level compared to mRNA-1273, although the statistically significance was reached only in the group without previous infection.

The results of the subgroup analyses on the anti-RBD IgG levels at T1 according to the steroids assumption and to the previous exposure to the SARS-CoV-2 are reported in Tables S6 and S7, respectively. An interaction between vaccine type and steroids was observed (P-value $= .0865$): a statistically significant negative impact of BNT162b2 vaccine on anti-RBD IgG level was detected only in patients receiving steroids.

In the subgroups of patients with and without a previous SARS-CoV-2 infection a similar impact of the type of vaccine was observed, with a higher immunogenicity of mRNA-1273 vaccine.

4 | DISCUSSION

Vaccination against SARS-CoV-2 is the most effective large-scale measure for the prevention of severe forms of COVID-19 in the general population,[28-30] as well as in vulnerable people, including cancer patients.[31] To date, the identification of predictors of vaccination response is warranted, because of the diffusion of new variants of SARS-CoV-2 and the high risk of COVID-19 complications in cancer patients.[32] Besides, the identification of nonresponders is crucial since other treatments, as monoclonal antibodies, are emerging. Tumor and treatment-related factors are implicated in the reduced vaccine immunogenicity.[22-27,31,33]

In contrast to previous reports, we simultaneously tested blood samples for three SARS-CoV-2 antibodies by a multiplex assay. In order to avoid the collection of false positives, common with the clinical assessment, measurement of IgG anti-N was used to identify a previous SARS-CoV-2 exposure. Moreover, the measurement of vaccination induced IgG, specific to S1 and RBD antigens of SARS-CoV-2, has increased the reliability of the immunogenicity assessment.

Our study confirmed a significantly lower antibody response to the COVID-19 mRNA-based vaccination in cancer patients at 30 days after the second dose; besides we found three major factors that significantly affected the humoral immune response in cancer patients.

First, the vaccination with mRNA-1273 has elicited a higher antibody response in cancer patients compared to BNT162b2. A possible explanation could be found in the higher mRNA content and in the longer administration interval between the two doses of mRNA-1273, compared to BNT162b2; however further studies on this issue are ongoing. Cancer patients are known to have a compromised immunity and this may implicate weaker responses to a lower amount of the immunogen. This result needs to be interpreted with caution for a number of different reasons. First of all, our study was not designed to compare the efficacy of the two vaccines. Moreover, the two groups of cancer patients were not balanced in number and characteristics, and no randomization was performed. However, similar to our results, other studies in general population, oncologic and multiple sclerosis patients reported a higher antibody response to mRNA-1273 vaccine compared to BNT162b2.[34-37]

Second, in our study, the presence of multiple comorbidities was another significant negative predictor of vaccine response. Indeed comorbidities (such as chronic obstructive pulmonary disease, chronic kidney disease, cardiovascular disease, diabetes and obesity) are well known negative prognostic factors for COVID-19 outcome[38] and are associated to a less effective immune response to vaccination.[39] Thus, health policies have paid particular attention to these categories and prioritized vaccine administration in national campaigns. A limit of our study was the lack of data collection about type and seriousness of chronic diseases useful to stratify frail patients. Third, in our cohort of cancer patients 31 subjects were exposed to SARS-CoV-2 before or during the time between first and second dose of vaccine. To date, few published studies report data regarding serological response in previously infected cancer patients, a subset that could be highly informative of the immune system of this vulnerable population. We showed that previous exposure to the virus significantly enhanced the response rate and the levels of the IgG against S1 and RBD antigens 30 days after the second dose of the vaccine. The effect of a previous exposure to the virus overwhelms the negative influence of any other condition, except for the use of G-CSF. Currently, there is a weak knowledge of the immunological mechanism underlying vaccination

response in previously infected individuals, the so called "hybrid immunity."[40] For this reason, similar studies are needed to dissect the underlying biological mechanisms. These considerations can be of special interest in light of the developments and preparations of new COVID-19 vaccines.

A further observation is that the use of G-CSF had significantly reduced the amount of anti-S1 IgG response. Probably, the plausible reason of this lack of response may be attributed to the iatrogenic myelotoxicity and the related immunocompromised status of patients receiving specific regimens and G-CSF acts as a surrogate marker of such conditions. Nevertheless, in our study, the myelotoxic potential of different antiblastic treatments was not recorded, and the active treatments did not negatively affect the seroconversion in the final analysis. Notably, the use of G-CSF should not be avoided in cancer patients during vaccination period.

We found only a trend towards a negative effect of the use of steroids. In our data collection, we did not stratify for the doses and type of steroids used. In addition, we did not exclude steroids administered as ancillary drug in chemotherapy regimens. Previous studies have frequently reported a negative effect of steroids but our study could not confirm nor invalidate these observations.

Several studies showed that solid tumor patients who were vaccinated while undergoing chemotherapy had decreased neutralizing capacity after two doses of COVID-19 vaccine.[41]

It should be noted that authors divided treatments with heterogenous methodology, frequently forming small groups. Furthermore, no information was provided about dose, number of cycles and myelotoxic effect of the treatments. By contrast our study, like others, did not evidence antiblastic treatment, specifically chemotherapy, as a risk factor of reduced neutralizing antibodies response after the primary course of COVID-19 vaccine.[42]

Our study is probably underpowered to establish the impact of anticancer therapy on vaccine immunogenicity. Further studies are investigating the role of additional booster vaccination (third and fourth dose) in improving antibody response and vaccine efficacy in cancer patients on active treatment.

This trial has a strength point on the timing of administration of the vaccines, not previously reported. All patients received vaccination before starting anticancer therapy or on the first day of the treatment cycle, in order to maintain a homogeneous response to antigen stimulation. The univariable and multivariable regression analysis did not show any impact on vaccine immune response of the active antiblastic therapy. The type of treatment and to be vaccinated during the active treatment or after the first cycle of therapy did not influence this result. Thus, the timing of vaccination could have mitigated the influence of treatment on the immune system of the patients.

To note, about 70% of enrolled patients were females: these data reflect the main expertise of our center, especially involved in the treatment of female malignancy (breast and gynecological cancer). On the other hand, this imbalance in the study population must be taken into consideration in evaluating immunogenicity because of the potential role of sex in COVID-19 vaccine efficacy.[43]

Our study has some limitations. Vaccine response was measured only at 30 days after the second dose. The assessment of response duration was not an objective of the study and this could affect the results in terms of an immunogenicity overestimation, as antibody titers could significantly decrease over time.[44] On the other hand, currently, third and fourth doses of mRNA-based vaccine are highly recommended for cancer patients. These additional boosters might elicit a further immunization, thus conferring adequate protection against SARS-CoV-2. Finally, further immunological mechanisms different from humoral immunity could also determine the protection against SARS-CoV-2 infection. In addition, in our study, the low number of subjects in the control group has not allowed to match them with cancer patients for age, sex and type of vaccine used. Nevertheless, the results are consistent with the literature data regarding seroconversion in the general population.[17,18]

Our study enriches the current knowledge regarding the immunogenicity of BNT162b2 and mRNA-1273 in patients with cancer with or without a previous exposure to the virus, exploring it in the early period after the second dose. Vaccine immunogenicity in cancer patients with a previous exposure to SARS-CoV-2 seems comparable to the healthy controls. Patients receiving highly myelotoxic treatments or comorbid need particular attention and specific counseling for their vaccination timing and vaccine selection.

To date, no reliable correlation is found between serum conversion and clinical efficacy of vaccination.[41] At present, there is no recommendation about routine assessment of serum antibodies, as a tool in selection of less proficient immune system patients (eg, HIV positive, hematologic malignancy, immunosuppressive therapies) in order to identify who could benefit from prophylactic medication.[45] Further studies are needed to unravel the biology of "hybrid immunity" against SARS-CoV-2 and to explore the best timing of vaccine administration.

AUTHOR CONTRIBUTIONS

Nicla La Verde: Conceptualization, data curation, investigation, methodology, project administration, resources, supervision, validation, visualization, writing—review & editing; **Agostino Riva:** Conceptualization, data curation, funding acquisition, methodology, project administration, resources, supervision, validation, visualization, writing—review & editing. **Maria Silvia Cona:** Conceptualization, data curation, investigation, visualization, writing—original draft. **Arianna Gabrieli:** data curation, investigation, project administration, supervision, validation. **Monica Cattaneo:** Data curation, investigation, resources. **Cinzia Fasola:** Data curation, investigation, methodology, resources. **Giuseppe Lipari:** Data curation, investigation. **Claudia De Stradis:** Data curation, investigation. **Valentina Favorito:** Data curation, investigation, resources. **Benedetta Lombardi Stocchetti:** Data curation, investigation, resources. **Davide Chizzoniti:** Data curation. **Alice Covizzi:** Data curation, investigation, validation. **Eliana Rulli:** Formal analysis, software, supervision, validation, visualization. **Francesca Galli:** Formal analysis, software, visualization. **Lorenzo Ruggieri:** Conceptualization, visualization, writing—review & editing. **Anna Gambaro:** Investigation, resources. **Sabrina Ferrario:** Investigation, resources. **Davide Dalu:**

Conceptualization, data curation, investigation, methodology, project administration, resources, supervision, validation, visualization, writing—review & editing. **Maciej S. Tarkowski:** Conceptualization, data curation, investigation, methodology, project administration, resources, supervision, validation, visualization, writing—original draft. The work reported in the article has been performed by the authors, unless clearly specified in the text.

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CONFLICT OF INTEREST

Nicla La Verde reports grant from Eisai; speaker bureau from GSK, travel expenses for conference from Gentili, Celgene, Pfizer; advisory role from Novartis and Celgene; advisor role, travel expenses for conference from Pfizer; advisory board from MSD, Roche, Novartis, Astrazeneca. Davide Dalu reports receiving grants from Gentili, travel expenses from Roche, Gentili, Eisai. There are no other personal or financial conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

The data generated in our study are available upon request from the corresponding author.

ETHICS STATEMENT

The study protocol was approved by the Istituto Spallanzani Ethical Committee and AIFA (number 312 of the experimental registry 2020/2021) and conducted according to the principles of the Declaration of Helsinki. All the participants signed written informed consent before any study procedure. All subject data were anonymized as required by the Italian Data Protection Code (Legislative Decree 196/2003) and the general authorizations issued by the Italian Data Protection Authority.

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REFERENCES

1. Cucinotta D, Vanelli M. WHO declares COVID-19 a pandemic. *Acta Biomed*. 2020;91:157-160.
2. Al-Omari A, Rabaan AA, Salih S, Al-Tawfiq JA, Memish ZA. MERS coronavirus outbreak: implications for emerging viral infections. *Diagn Microbiol Infect Dis*. 2019;93:265-285.
3. Luk HKH, Li X, Fung J, Lau SKP, Woo PCY. Molecular epidemiology, evolution and phylogeny of SARS coronavirus. *Infect Genet Evol*. 2019;71:21-30.
4. Wang Q, Zhang Y, Wu L, et al. Structural and functional basis of SARS-CoV-2 entry by using human ACE2. *Cell*. 2020;181:894-904.
5. Alicandro G, Remuzzi G, La Vecchia C. Italy's first wave of the COVID-19 pandemic has ended: no excess mortality in May, 2020. *Lancet*. 2020;396:e27-e28.
6. Johns Hopkins Coronavirus Resource Center. COVID-19 Map [Internet]. https://coronavirus.jhu.edu/map.html. Accessed 3 April 2022.
7. Sharafeldin N, Bates B, Song Q, et al. Outcomes of COVID-19 in patients with cancer: report from the national COVID cohort collaborative (N3C). Publisher [Internet]; 2021. https://scholarworks.iupui.edu/handle/1805/27037. Accessed 3 April 2022.
8. Garassino MC, Whisenant JG, Huang L-C, et al. COVID-19 in patients with thoracic malignancies (TERAVOLT): first results of an international, registry-based, cohort study. *Lancet Oncol*. 2020;21:914-922.
9. Saini KS, Tagliamento M, Lambertini M, et al. Mortality in patients with cancer and coronavirus disease 2019: a systematic review and pooled analysis of 52 studies. *Eur J Cancer*. 2020;139:43-50.
10. Zhou Y, Yang Q, Chi J, et al. Comorbidities and the risk of severe or fatal outcomes associated with coronavirus disease 2019: a systematic review and meta-analysis. *Int J Infect Dis*. 2020;99:47-56.
11. Chavez-MacGregor M, Lei X, Zhao H, Scheet P, Giordano SH. Evaluation of COVID-19 mortality and adverse outcomes in US patients with or without cancer. *JAMA Oncol*. 2022;8:69-78.
12. Lee LY, Cazier J-B, Angelis V, et al. COVID-19 mortality in patients with cancer on chemotherapy or other anticancer treatments: a prospective cohort study. *Lancet*. 2020;395:1919-1926.
13. Kuderer NM, Choueiri TK, Shah DP, et al. Clinical impact of COVID-19 on patients with cancer (CCC19): a cohort study. *Lancet*. 2020;395:1907-1918.
14. Cona MS, Rulli E, Dalu D, et al. The emotional impact of the COVID-19 outbreak on cancer outpatients and their caregivers: results of a survey conducted in the midst of the Italian pandemic. *Support Care Cancer*. 2022;30(2):1115-1125. doi:10.1007/s00520-021-06489-y
15. Berardi R, Torniai M, Cona MS, et al. Women for oncology Italy. Social distress among medical oncologists and other healthcare professionals during the first wave of COVID-19 pandemic in Italy. *ESMO Open*. 2021;6(2):100053. doi:10.1016/j.esmoop.2021.100053
16. Dalu D, Rota S, Cona MS, et al. A proposal of a "ready to use" COVID-19 control strategy in an oncology ward: Utopia or reality? *Crit Rev Oncol Hematol*. 2021;157:103168.
17. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N Engl J Med*. 2020;383:2603-2615.
18. Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N Engl J Med*. 2021;384:403-416.
19. Dagan N, Barda N, Kepten E, et al. BNT162b2 mRNA Covid-19 vaccine in a nationwide mass vaccination setting. *N Engl J Med*. 2021;384:1412-1423.
20. Thompson MG, Burgess JL, Naleway AL, et al. Interim estimates of vaccine effectiveness of BNT162b2 and mRNA-1273 COVID-19 vaccines in preventing SARS-CoV-2 infection among health care personnel, first responders, and other essential and frontline workers - eight U.S. locations, December 2020-March 2021. *MMWR Morb Mortal Wkly Rep*. 2021;70:495-500.
21. Dickerman BA, Gerlovin H, Madenci AL, et al. Comparative effectiveness of BNT162b2 and mRNA-1273 vaccines in U.S. veterans. *N Engl J Med*. 2022;386:105-115.
22. Monin L, Laing AG, Muñoz-Ruiz M, et al. Safety and immunogenicity of one versus two doses of the COVID-19 vaccine BNT162b2 for patients with cancer: interim analysis of a prospective observational study. *Lancet Oncol*. 2021;22:765-778.
23. Massarweh A, Eliakim-Raz N, Stemmer A, et al. Evaluation of seropositivity following BNT162b2 messenger RNA vaccination for SARS-CoV-2 in patients undergoing treatment for cancer. *JAMA Oncol*. 2021;7:1133-1140.
24. Cavanna L, Citterio C, Biasini C, et al. COVID-19 vaccines in adult cancer patients with solid tumours undergoing active treatment:

seropositivity and safety. A prospective observational study in Italy. *Eur J Cancer*. 2021;157:441-449.
25. Lee LYW, Starkey T, Ionescu MC, et al. Vaccine effectiveness against COVID-19 breakthrough infections in patients with cancer (UKCCEP): a population-based test-negative case-control study. *Lancet Oncol*. 2022;23:748-757.
26. Herzog Tzarfati K, Gutwein O, Apel A, et al. BNT162b2 COVID-19 vaccine is significantly less effective in patients with hematologic malignancies. *Am J Hematol*. 2021;96:1195-1203.
27. Di Noia V, Pimpinelli F, Renna D, et al. Immunogenicity and safety of COVID-19 vaccine BNT162b2 for patients with solid cancer: a large cohort prospective study from a single institution. *Clin Cancer Res*. 2021;27:6815-6823.
28. Gilbert PB, Montefiori DC, McDermott AB, et al. Immune correlates analysis of the mRNA-1273 COVID-19 vaccine efficacy clinical trial. *Science*. 2022;375:43-50.
29. CDC. COVID Data Tracker [Internet]; 2020. https://covid.cdc.gov/covid-data-tracker. Accessed 3 April 2022.
30. Pezzotti P, Fabiani M, Filia A, et al. This report was produced by the ISS Working Group and the "COVID-19 vaccine surveillance system" of the Ministry of Health: 21.
31. Wu JT-Y, La J, Branch-Elliman W, et al. Association of COVID-19 vaccination with SARS-CoV-2 infection in patients with cancer: a US Nationwide Veterans Affairs Study. *JAMA Oncol*. 2022;8:281-286.
32. Schmidt AL, Labaki C, Hsu C-Y, et al. COVID-19 vaccination and breakthrough infections in patients with cancer. *Ann Oncol*. 2022;33:340-346.
33. Amatu A, Pani A, Patelli G, et al. Impaired seroconversion after SARS-CoV-2 mRNA vaccines in patients with solid tumours receiving anticancer treatment. *Eur J Cancer*. 2022;163:16-25.
34. Sormani MP, Inglese M, Schiavetti I, et al. Effect of SARS-CoV-2 mRNA vaccination in MS patients treated with disease modifying therapies. *EBioMedicine*. 2021;72:103581.
35. Self WH. Comparative effectiveness of Moderna, Pfizer-BioNTech, and Janssen (Johnson & Johnson) vaccines in preventing COVID-19 hospitalizations among adults without immunocompromising conditions: United States, March-August 2021. *MMWR Morb Mortal Wkly Rep*. 2021;70:1337-1343. doi:10.15585/mmwr.mm7038e1.
36. Steensels D, Pierlet N, Penders J, Mesotten D, Heylen L. Comparison of SARS-CoV-2 antibody response following vaccination with BNT162b2 and mRNA-1273. *JAMA*. 2021;326:1533-1535.
37. Figueiredo JC, Merin NM, Hamid O, et al. Longitudinal SARS-CoV-2 mRNA vaccine-induced humoral immune responses in patients with cancer. *Cancer Res*. 2021;81:6273-6280.
38. Izcovich A, Ragusa MA, Tortosa F, et al. Prognostic factors for severity and mortality in patients infected with COVID-19: a systematic review. *PLoS One*. 2020;15:e0241955.
39. Kovaiou RD, Herndler-Brandstetter D, Grubeck-Loebenstein B. Age-related changes in immunity: implications for vaccination in the elderly. *Expert Rev Mol Med*. 2007;9:1-17.
40. Crotty S. Hybrid immunity. *Science*. 2021;372:1392-1393.
41. Fendler A, de Vries EGE, GeurtsvanKessel CH, et al. COVID-19 vaccines in patients with cancer: immunogenicity, efficacy and safety. *Nat Rev Clin Oncol*. 2022;19:385-401.
42. Fendler A, Shepherd STC, Au L, et al. Adaptive immunity and neutralizing antibodies against SARS-CoV-2 variants of concern following vaccination in patients with cancer: the CAPTURE study. *Nat Cancer*. 2021;2:1305-1320.
43. Bignucolo A, Scarabel L, Mezzalira S, Polesel J, Cecchin E, Toffoli G. Sex disparities in efficacy in COVID-19 vaccines: a systematic review and meta-analysis. *Vaccine*. 2021;9:825.
44. Nelli F, Fabbri A, Onorato A, et al. Six month immunogenicity of COVID-19 mRNA-BNT162b2 vaccine in actively treated cancer patients: updated results of the Vax-On study. *Ann Oncol*. 2022;33:352-354.
45. Levin MJ, Ustianowski A, De Wit S, et al. Intramuscular AZD7442 (Tixagevimab-Cilgavimab) for prevention of COVID-19. *N Engl J Med*. 2022;386:2188-2200.

SUPPORTING INFORMATION

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

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