Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

European Journal of Cancer 170 (2022) 149–157

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

The national COVID-19 vaccination campaign targeting the extremely vulnerable: the Florence Medical Oncology Unit experience in patients with cancer

Maria S. Pino [a,*], Simone Cheli [b], Marco Perna [a], Valentina Fabbroni [a], Clara Giordano [a], Francesca Martella [a], Fabio Lanini [a], Angela S. Ribecco [a], Silvia Scoccianti [c], Carlotta Bacci [a], Valentina Baldazzi [a], Ilaria Bertolini [a], Greta Di Leonardo [a], Chiara Fulignati [a], Raffaella Grifoni [a], Elena Molinara [a], Sheila Rangan [a], Renato Tassi [a], Federica Furlan [d], Gil Goldzweig [e], Andrea Bassetti [d], Luisa Fioretto [a]

[a] *Medical Oncology Unit - Florence, Department of Oncology, Azienda USL Toscana Centro, Italy*
[b] *School of Human Health Sciences, University of Florence, Italy*
[c] *Radiation Oncology Unit - Florence, Department of Oncology, Azienda USL Toscana Centro, Italy*
[d] *Direzione Sanitaria, Santa Maria Annunziata Hospital, Azienda USL Toscana Centro, Italy*
[e] *The Academic College of Tel Aviv - Yaffo, Tel Aviv, Israel*

Received 30 January 2022; received in revised form 19 March 2022; accepted 1 April 2022
Available online 20 April 2022

KEYWORDS
COVID-19;
Vaccination;
Safety

Abstract ***Background:*** International and national oncology societies had released recommendations in favor of COVID-19 vaccination in cancer patients. In the context of the national vaccination campaign targeting the so called extremely vulnerable, we aimed to assess the safety and efficacy of the mRNA vaccines in a cohort of 623 patients.
Methods: Between March 26 and April 04, 2021, the Pfizer and BioNTech BNT162b2 mRNA and the Moderna mRNA-1273 vaccines were given as a two-dose prime-boost regimen. Starting on September 25th 2021 a third dose was offered to patients in whom a suboptimal immunogenicity with COVID-19 vaccination could be expected. Safety assessments were performed by phone call 7 days after each dose. Electronic health records were accessed to review demographic information, disease history, treatment detail, and outcome events of participants patients'.

* *Corresponding author*: Vice-Director Medical Oncology Unit in Florence, Santa Maria Annunziata Hospital, Department of Oncology, Azienda USL Toscana Centro, 50012 Florence, Italy.
E-mail address: Mariasimona.pino@uslcentro.toscana.it (M.S. Pino).

https://doi.org/10.1016/j.ejca.2022.04.008

Findings: No toxicities were reported in 63.7%, 54%, and in 48.7% patients with cancer after each dose. Mild-to-moderate pain at the injection site was the most commonly adverse event. After the second dose, 46% of the 610 patients reported toxicity, with more systemic side-effects observed. Fever was reported in 45% of patients, with a temperature $\geq$ 38 °C in 21.4% of them. Of the 335 patients receiving a third vaccine dose, 51% reported toxicity, with 13% of patients reporting more than one effect. Logistic regression analysis reported mixed results, with limited variables or categories reporting a significant odd ratio. The type of vaccine reported a significant value at first dose (OR = 0.12; CI 0.52, 0.26; p = 0.00). Thirty-four cases of COVID-19 infection were reported with only one patient requiring a short-term hospitalization for monitoring.
Interpretation: The safety profile of the mRNA vaccines does not raise any specific concerns and support prioritization of vaccination for cancer patients.

1. Introduction

About two year after its onset, the SARS-CoV-2 pandemic has recorded 326.286.532 cases and 5.536.789 deaths worldwide [1]. Among the worst-hit countries, Italy developed its strategic plan for anti-SARS-CoV-2/COVID-19 vaccination well in advance and identified priority target groups for COVID-19 vaccines at different stages of supply availability [2]. The risk of infection, severe illness, and death due to COVID-19 are higher among patients with cancer compared to the general population [3–11]. In March 2021, the Italian governments and authorities at national and regional levels have prioritized COVID-19 vaccinations for cancer patients.

Although vaccinations in cancer patients undergoing active treatment may be less effective in preventing infections, vaccination practice is generally able to decreased duration and severity of the infection and potentially to improve morbidity and mortality even in potentially compromised patients [12,13]. Moreover, as immunocompromised individuals might be a source of prolonged viral shedding and could contribute to the onset of virus variants, the vaccination of patients with cancer is a key part of the public health management. On this basis, and despite most of the registry trials of COVID-19 vaccines excluded patients with active malignancies, or those receiving systemic anticancer therapies, international and national oncology societies had released recommendations in favor of COVID-19 vaccination, regardless of treatment type or underlying cancer [14–16]. Furthermore, based on the few studies that have specifically reported on vaccine safety outcomes in patients with cancer receiving treatment, no safety concerns have been reported so far [17–20].

In the context of the national vaccination campaign targeting the so called extremely vulnerable, we aimed to address the safety and efficacy of the mRNA vaccines in a cohort of patients with solid tumors.

2. Methods

2.1. Participants and study design

According to the National Italian Cancer Vaccination Strategy for the extremely vulnerable individuals, cancer patients on systemic antitumor treatment, or whose treatment has been completed in the last 6 months, or having an active advanced disease, were considered eligible for vaccination regardless of disease stage, performance status, or life expectancy [2]. Between March 26 and April 04, 2021, vaccination was offered to patients followed at the Medical Oncology Unit in Florence at Santa Maria Annunziata, Serristori and Borgo San Lorenzo Hospitals. Adherence to SARS-CoV-2 vaccine and reasons of refusal were collected. The Pfizer and BioNTech BNT162b2 mRNA and the Moderna mRNA-1273 vaccines were given as a two-dose prime-boost regimen 21 days (for BNT162b2) or 28 days (for mRNA-1273) apart [4,21,22]. Patients who were previously infected with SARS-CoV-2 were excluded if the infection occurred in the 3 months before. If the patient had been infected between 3 and 6 months before, only one full dose was administered.

On September 9, the Technical-Scientific Commission of AIFA (Italian Medicines Agency) recommended that individuals with certain immunocompromising conditions who received a two-dose mRNA vaccine series receive a third dose as part of the primary vaccine series [23]. Starting on September 25, 2021 we offered a third dose to patients on systemic antitumor treatment during COVID-19 vaccination or whose treatment has been completed in the last 6 months before vaccination. Safety assessments were performed by phone call 7 days after each dose for collecting data regarding solicited local and systemic adverse reactions. Solicited adverse events recorded were pain at injection site, sore arm, local erythema, fever, fatigue, headaches, chills, arthralgia,

myalgia, diarrhoea, nausea, vomiting, flu-like symptoms, and lymphadenopathy. Unsolicited adverse events were collected within 28 days after each dose. Adverse events were graded according to a standard toxicity grading scale [24]. Electronic health records were accessed by the study investigators to review demographic information, disease history, treatment detail, and outcome events of participants patients'. Positive cases of SARS-CoV-2 infection were extracted from the COVID-19 integrated surveillance system of the National Institute of Health, on March 10, 2022. The study was approved by the institutional review board.

2.2. Statistical analysis

A logistic regression analysis predicting acute side effects after anti-COVID-19 vaccine (dependent variable; 0 = No side effects; 1 = Reported side-effects) was performed. We included as independent variables: type of cancer; no evidence of disease (NED) versus metastatic cancer; being under treatment versus follow-up; type of treatment; type of vaccine (the Moderna mRNA-1273 and the Pfizer and BioNTech BNT162b2 mRNA). The logistic regression analysis was performed for each dose (1st dose; 2nd dose; 3rd dose) using a simple contrast for categorical variable to explore odd ratio (OR). Finally, a general linear model (GLM) with repeated measures was performed to explore how doses interact with significant predictors of linear regression analysis over time. The continuous score of side effects across the three doses was included as a unique factor comprising the within-subjects variables (side effect at 1st dose, 2nd dose, 3rd dose, respectively). A repeated contrast was used for the entire variables included in the model, using the first category as the reference one. In order to explore the comparison between the 1st dose and the 3rd dose a second GLM model was performed applying a simple contrast. All the analyses were conducted through SPSS version 25.

3. Results

The initial cohort included 911 patients, which were contacted via phone by the Hospital's care to schedule a vaccination appointment. 187 (20%) patients were already vaccinated belonging to other prioritized groups, 47 (5%) patients refused vaccination, mostly due to fear of side-effects, 48 (5%) patients could not be reached, and 11 (1%) patients had developed the disease less than 3 months before. The patients who refused vaccination on the first contact were called a second time after two weeks and 6 patient scheduled then a vaccination appointment, with a total refusal rate of 4.5%. As shown in Table 1, the final cohort comprised 623 patients, 225 (36.1%) men and 398 (63.9%) women, with a mean age of 66.41 and 71.43 years, respectively.

Table 1
Descriptives of the sample

Age (in years) mean ± SD	65.95 ± 11.51
Gender n (in %)	
Male	225 (36.1%)
Female	398 (63.9%)
Current condition n (in %)	
Alive	580 (93.1%)
Deceased	43 (6.9%)
Group tumor n (in %)	
Breast cancer	211 (33.9%)
Melanoma/skin cancer	111 (17.8%)
Gastrointestinal	94 (15.1%)
Genitourinary	69 (11.1%)
Gynecological	55 (8.8%)
Lung	43 (6.9%)
Other[a]	40 (6.4%)
Stage n (in %)	
NED (no evidence of disease)	316 (50.7%)
Metastatic	307 (49.3%)
Ongoing therapy during vax period n (in %)	
Yes	462 (74.2%)
No	161 (25.8%)
Type of treatment n (in %)	
Chemotherapy	164 (35.5%)
Immunotherapy	82 (17.7%)
Hormone therapy	82 (17.7%)
Target therapy	76 (16.5%)
Chemotherapy - Target therapy	39 (8.4%)
Target - Hormone therapy	11 (2.4%)
Other treatment[b]	8 (1.8%)
Group treatment n (in %)	
Chemotherapy	204 (32.7%)
Other	258 (41.4%)
Follow up	161 (25.9%)

[a] Other primary cancer diagnoses within our cohort: neuroendocrine (n = 1), head and neck (n = 13), central nervous system (n = 17), gastrointestinal stromal (n = 5), and peritoneal (n = 2) tumors, sarcoma (n = 2).
[b] Other treatment within our cohort: bifosfonate (n = 6), chemio-immune therapy (n = 1), immune-target therapy (n = 1).

The most frequent primary tumors were breast and melanoma/skin cancer [211 (33.9%) and 111 (17.8%)], respectively, followed by gastrointestinal [94 (15.1%)], genitourinary [69 (11.1%)], gynecologic [55 (8.8%)] and lung cancer [43 (6.9%)]. Treatment was ongoing in 462 patients (74.2%), whereas it was completed in the previous 3 months or 6 months for 20 (3.2%) and 45 (7.2%) patients, respectively. Active treatment were about to start in 26 (4.2%) patients. Treatment protocols consisted of chemotherapy in 204 patients (44%), immunotherapy in 82 (17.7%) patients, target therapy in 87 (18.8%) patients and hormone therapy for metastatic disease in 82 (17.7%) patients. Adjuvant hormone therapy was carried out by 43 (52.4%) patients. Patients treated with chemotherapy alone were 164 (80.4%), while chemotherapy was added to a target agent or immunotherapy in 39 (19.1%) and in 1 (0.5%) patients, respectively. Target therapy was prescribed alone in 76 (87.3%) patients and with hormone therapy in 11 (12.7%) patients. Based on vaccine availability, between

March 27 and April 10, 512 patients received the Moderna mRNA-1273 vaccine, between April 16 and 27, 91 patients received the Pfizer BNT162b2 mRNA vaccine, while the last 20 patients were vaccinated between May 1 and May 09, with the Moderna mRNA-1273 vaccine in 15 and the Pfizer BNT162b2 mRNA vaccine in 5 cases, respectively. Altogether we administered 527 (84.6%) doses of Moderna mRNA-1273 vaccine and 96 (15.4%) doses of Pfizer BNT162b2 mRNA vaccine.

As shown in Figs. 1 and 2, 226 (36.3%) of 623 patients with cancer reported toxicities following the first dose of vaccines. The most common side-effects were local, with 129 (57.1%) patients reporting mild-to-moderate pain at the injection site within hours to several days after the injection. Two patients reported severe pain at the injection site and injection-site redness and swelling, respectively. The most commonly reported systemic side-effects included fatigue [34 (15.1%)], headache [18 (8%)], muscle and joint pain [13 (5.8%)], while 2.2% of the patients reported a fever event with temperature $\geq$ 38 °C.

Thirteen patients (2%) did not receive the second vaccine dose: 7 patients because of previous SARS-COV-2 infection, 3 patients died after the first dose due to disease progression, 2 patients refused the second dose due to fear of adverse events, and 1 patient contracted SARS-CoV-2 infection after the first dose. After the second dose, 281 (46%) of the 610 patients reported toxicity, with more systemic side-effects observed. Pain at the injection site was reported in 20 patients (7.1%), whereas the most common systemic side effects were muscle and joint pain [52 (18.5%)], headache [32 (11.4%)], fatigue [24 (8.5%)], and chills [18 (6.4%)]. A fever event was reported in 126 (45%) patients, with a temperature $\geq$ 38 °C in 21.4% of them within the first 1–2 days after vaccination and resolved shortly thereafter. None of the reported side-effects required hospital admission or any other special intervention.

Of the 335 patients receiving a third vaccine dose, 172 (51%) reported toxicity, with 22 (13%) patients reporting more than one effect. Fever was reported in 95 (55%) patients, with a temperature $\geq$ 38 °C in 56% of them, lasting more than 24 h in 66%. Pain at the injection site was reported in 58 patients (34%).

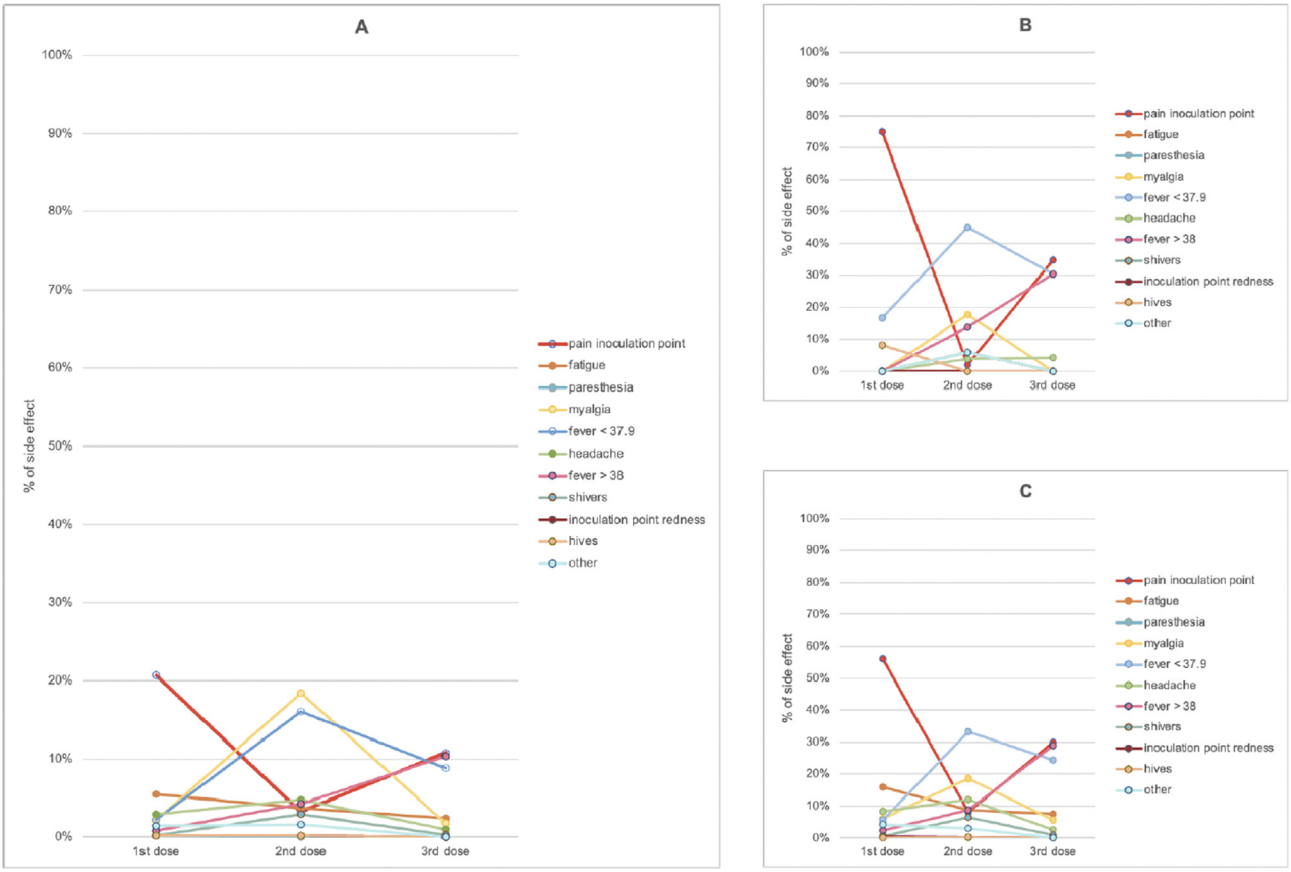

Fig. 1. Proportion of different side effects
Note: We report the proportion (%) of different side effects in the whole sample (A), and in the sub-samples of those vaccinated with either the Pfizer and BioNTech BNT162b2 mRNA (B) or the Moderna mRNA-1273 vaccines (C).

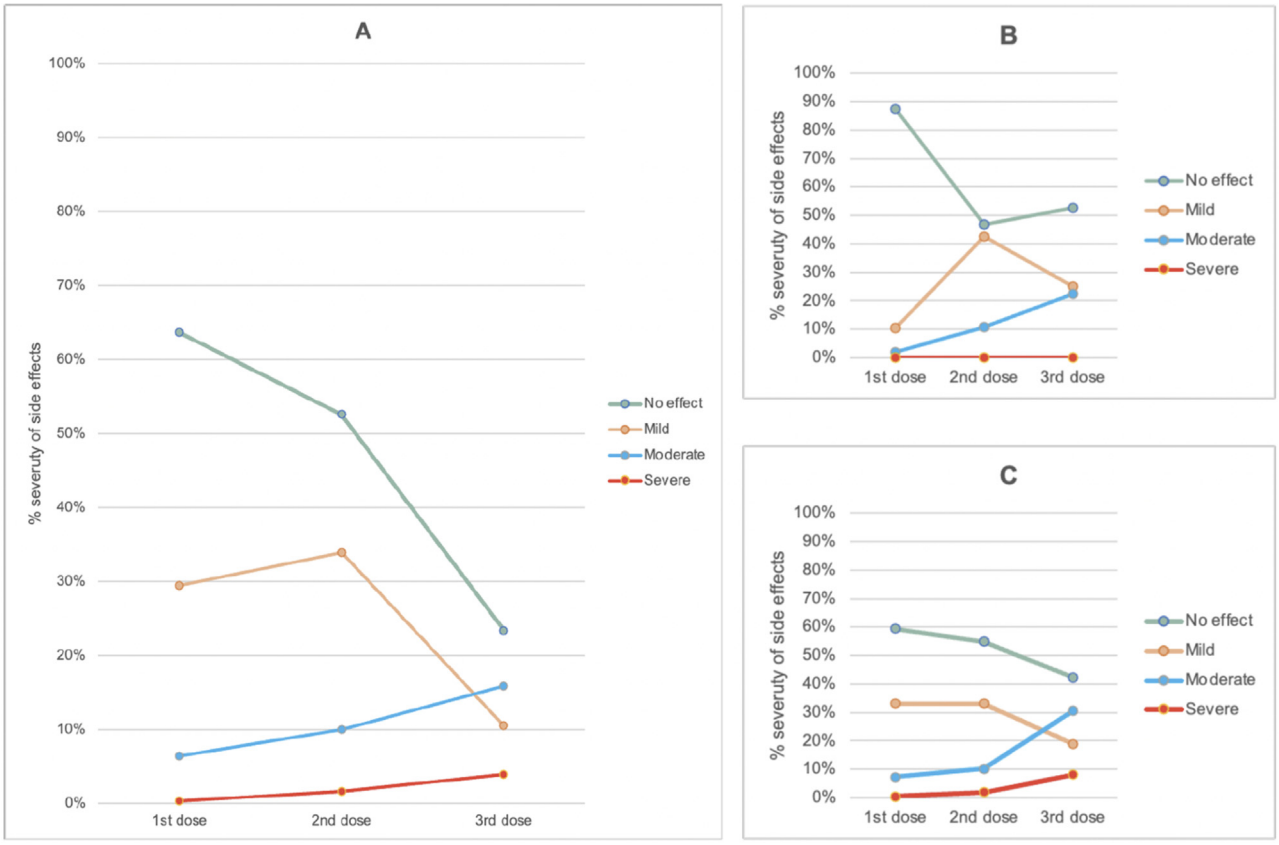

Fig. 2. Severity of side effects
Note: We report the proportion (%) of level of severity of side effects in the whole sample (A), and in the sub-samples of those vaccinated with either the Pfizer and BioNTech BNT162b2 mRNA (B) or the Moderna mRNA-1273 vaccines (C).

Table 2
Side effects across doses

Effects after 1st shot n (%)	
Yes	226 (36.3%)
No	397 (63.7%)
Type of effect after 1st shot n (%)	
Pain injection site	129 (57.1%)
Fatigue	34 (15.1%)
Paresthesia	1 (0.4%)
Myalgia	13 (5.8%)
Fever <37.9	14 (6.2%)
Headache	18 (8%)
Fever >38	5 (2.2%)
Shivers	1 (0.4%)
Injection-site redness	1 (0.4%)
Hives	1 (0.4%)
Other	9 (4%)
Severity of side effect after 1st shot mean ± SD	0.43 ± 0.63
No effect	397 (63.7%)
Mild	184 (29.5%)
Moderate	40 (6.4%)
Severe	2 (0.3%)
Effects after 2nd shot n (in %)	281 (46%)
Yes	329 (54%)
No	
Type of effect after 2nd shot n (in %)	
Pain inoculation point	20 (7.1%)
Fatigue	24 (8.5%)
Myalgia	52 (18.5%)

Table 2 (*continued*)

Fever <37.9	99 (35.2%)
Headache	32 (11.4%)
Fever >38	27 (9.6%)
Shivers	18 (6.4%)
Inoculation point redness	1 (0.4%)
Hives	1 (0.4%)
Other	7 (2.5%)
Severity of side effect after 2nd shot mean ± SD	0.90 ± 0.75
No effect	329 (54%)
Mild	209 (34.2%)
Moderate	62 (10.2%)
Severe	10 (1.6%)
Effects after 3rd shot n (in %)	
Yes	172 (51.3%)
No	163 (48.7%)
Type of effect after 3rd shot n (in %)	
Pain inoculation point	58 (33.7%)
Fatigue	6 (3.5%)
Myalgia	20 (11.6%)
Fever <37.9	42 (24.4%)
Headache	6 (3.5%)
Fever >38	53 (30.8%)
Shivers	2 (1.2%)
Other	1 (0.6%)
Severity of side effect after 3rd shot mean ± SD	0.63 ± 0.94
No effect	163 (49%)
Mild	57 (17%)
Moderate	91 (27%)
Severe	24 (7%)

Table 3
Summary of logistic regression analysis predicting acute side effects

Variable	*B*	*SE*	*OR*	95% CI	Wald statistic	*p*
First dose						
Sex	- 0.99	0.29	0.37	[0.21, 0.65]	11.99	0.00
Alive/deceased	- 0.46	0.42	0.63	[0.28, 1.44]	1.21	0.27
Breast cancer vs Melanoma/skin cancer	22.08	21971.91	3.865E + 9	[0.00,.]	0.00	0.99
Breast cancer vs Lung cancer	0.58	1.56	1.78	[0.08, 37.49]	0.14	0.71
Breast cancer vs Other	0.44	1.33	1.55	[0.11, 21.14]	0.11	0.74
NED/metastatic	0.55	0.24	1.72	[1.07, 2.78]	5.03	0.03
No/Yes	- 0.25	0.38	0.78	[0.37, 1.62]	0.44	0.51
Chemotherapy vs Follow-up	- 0.14	0.29	0.87	[0.49, 1.55]	0.22	0.64
Chemotherapy vs Other	0.56	0.41	1.75	[0.79, 3.89]	1.88	0.17
Type of vaccine	2.10	1.44	8.17	[3.70, 18.05]	27.03	**0.00**
Second dose						
Sex	- 0.02	0.25	0.98	[0.59, 1.61]	0.00	0.94
Alive/deceased	1.50	0.53	4.47	[1.59, 12.54]	8.08	0.00
Breast cancer vs Melanoma/skin cancer	18.44	11436.68	102091047	[0.00,.]	0.00	0.99
Breast cancer vs Lung cancer	17.13	11436.68	27570621.8	[0.00,.]	0.00	0.99
Breast cancer vs Other	17.85	11436.68	56432713.6	[0.00,.]	0.00	0.99
NED/metastatic	- 0.31	0.23	0.73	[0.47, 1.14]	1.91	0.17
No/Yes	0.07	0.36	1.07	[0.53, 2.17]	0.04	0.84
Chemotherapy vs Follow-up	0.11	0.28	1.11	[0.65, 1.91]	0.15	0.70
Chemotherapy vs Other	0.25	0.39	1.28	[0.60, 2.75]	0.40	0.53
Type of vaccine	- 0.25	0.25	0.78	[0.46, 1.28]	0.98	0.32
Third dose						
Sex	- 0.56	0.34	0.57	[0.30, 1.11]	2.72	0.10
Alive/Deceased	21.97	40192.73	3.477E + 9	[0.00,.]	0.00	1
Breast cancer vs Melanoma/skin cancer	44.75	49217.93	2.720E + 19	[0.00,.]	0.00	0.99
Breast cancer vs Lung cancer	22.73	28406.74	7.437E + 9	[0.00,.]	0.00	0.99
Breast cancer vs Other	22.48	28406.74	5.788E + 9	[0.00,.]	0.00	0.99
NED/metastatic	0.21	0.29	1.23	[0.69, 2.19]	0.50	0.48
No/Yes	- 1.25	0.99	0.29	[0.04, 2.01]	1.58	0.21
Chemotherapy vs Follow-up	0.22	0.37	1.24	[0.61, 2.54]	0.35	0.56
Chemotherapy vs Other	1.46	1.08	4.33	[0.52, 35.72]	1.85	0.17
Type of vaccine	0.65	0.40	1.91	[0.88, 4.16]	2.64	0.10

Note: * Simple contrast method with first category (breast cancer) as reference. ** Cancer Type: breast cancer, gastroenteric cancer, melanoma, lung cancer, genitourinary cancer, gynecological cancer, skin cancer, prostatic cancer, glioblastoma, other type of cancer.

Descriptives of side effects across the three doses are reported in Table 2. Logistic regression analysis reported mixed results, with limited variables or categories reporting a significant odd ratio as reported in Table 3. The type of vaccine reported a significant value at first dose (OR = 0.12; CI 0.52, 0.26; $p = 0.00$) but not at second and third dose. Finally, we explored the interaction over time between severity of side-effects and sex, age (cut-off $\geq$ 75), NED versus metastatic cancer, type of cancer. We did not find a significant effect both between and within subjects only for type of vaccine. The GLM model reported in Table 4 do not suggest an interaction

Table 4
Summary of general linear model

	Within-subjects contrasts						
Source	Doses	Mean Square	F	Sig	Partial eta square	Noncent. parameter	Observed power
Doses	Level 1 vs Level 2	13.73	17.63	0.00	0.05	17.63	0.99
	Level 2 vs Level 3	7.55	5.36	0.21	0.02	5.36	0.64
Doses *Vaccine	Level 1 vs Level 2	1.98	2.54	0.11	0.01	2.54	0.36
	Level 2 vs Level 3	3.41	2.42	0.12	0.01	2.42	0.34
	Between-subjects effects						
Source		Mean square	F	Sig	Partial eta square	Noncent. parameter	Observed power
Intercept		52.84	198.06	0.00	0.38	198.06	1
Vax type		1.33	4.99	0.03	0.02	4.99	0.61

Note: We included in the model as within-subjects factor the three continuous scores of severity of side-effects across the three doses (doses), and as between-subjects factor the type of vaccine (Moderna mRNA-1273 vs Pfizer BNT162b2 mRNA vaccine). Repeated contrast was used for all the variables.

over time, comparing Level 1 and 2, and Level 2 and 3. In order to compare Level 1 and 3 we also performed a GLM model using a simple contrast, but we did not find a significant interaction within subjects. Through the electronic medical records review, we identified 1 case of COVID-19 infection 23 days after the first Moderna mRNA-1273 vaccine dose and 4 cases after a median of 2.5 months after the second Moderna mRNA-1273 vaccine dose. One case of COVID-19 infection was reported 2.8 months after the second Pfizer BNT162b2 mRNA vaccine dose. Only one patient requires a short-term hospitalization. During the fourth wave of COVID-19, sustained by the very high transmission rate of the B.1.1.529 (omicron) variant, 28 patients experienced asymptomatic breakthrough infections, after a median time of 3.5 months (range 0.5–4.7 months) from the third vaccine dose (Moderna mRNA-1273 in 93% of the cases).

4. Conclusions

Our cohort study provides data on use of the SARS-CoV-2 mRNA vaccines in patients with cancer in the real-world setting. Despite the absence of evidence regarding the immunogenicity and safety of the available vaccines, anti-SARS-CoV-2 vaccination was offered to cancer patients in the Florence Medical Oncology Unit as part of the National and Regional Vaccination Campaign, as the expected benefits of vaccination significantly and substantially outweigh the potential risks.

One of the barriers to a successful vaccination program is the public hesitancy to get vaccinated because of the various misconceptions and apprehensions about vaccine safety and efficacy. Di Noia V. et al. reported on adherence to SARS-CoV-2 vaccine campaign in the context of a large Italian Comprehensive Cancer Center [25]. In this study 11.2% of the eligible patients refused vaccination and the refusal rate even rose to 19.7% after the suspension of the AstraZeneca vaccine was announced, highlighting the "infodemic" effect, caused by the media or social networks, on vaccine hesitancy and resistance. A French survey performed before the launch of the vaccination campaign had reported a refusal rate of 16.6%; the main reasons were lack of confidence in the scientific results, fear of side-effects and believing COVID-19 to be benign [26]. Another study, by Villarreal-Garza *et al.*, reported an even higher rate of refusal (34%) in a cohort of 540 women suffering from breast cancer [27]. To generate awareness and to provide correct, consistent and timely information the Department of Oncology (Azienda USL Toscana Centro), focused on communication and information to motivate cancer patients. We believe that this is the reason for the low first dose-refusal rate of 4.5%. Consistently with our hypothesis that correct information is the key to greater adherence to the vaccination campaign, a refusal rate of 20% was observed to the proposal of the third dose.

Based on the studies published to date, that have specifically reported on vaccine safety outcomes in patients with cancer receiving treatment, no safety concerns have been reported so far. Our study confirm that the mRNA vaccines are generally well tolerated in patients with cancer, even in those on immunotherapy who might have been anticipated to make exaggerated, inflammatory immune responses. A short-term safety report of the Pfizer BNT162b2 mRNA COVID-19 vaccine in 137 patients with cancer in Israel, treated with immune checkpoint inhibitors, provides some reassurance for their use in patients being treated with immune checkpoint inhibitors since no vaccine-related or immune checkpoint inhibitor-related severe adverse events have been observed [17]. Similarly no safety concerns emerged in our study. None of the variables considered in the regression models seem to show a high effect size in predicting side effects. The only variable showing significant interactions over time is the type of vaccine at first dose. This interaction does not persist over time. We do observe an increase in systemic adverse events and severity of adverse events across the three doses, likely related to the expected immune response to the vaccine. In a large prospective cohort study including 816 patients with cancer, multivariate analysis confirmed a statistically significant association between the incidence of any adverse events after the second dose and higher serologic response rate [28]. Patients with cancer tend to be cautious and adherent to recommended safety measures in their surrounding environment, such as social distancing and applying a facial mask, which may affect the low infection rate observed regardless of their vaccination effect. In our cohort we observed only 6 cases of COVID-19 infection, and it represented about the 1% of all the vaccinated patients. Only 1 of these patients required a short-term hospitalization for monitoring. This suggests great effectiveness and protection obtained with mRNA vaccines in cancer patients, and the result is aligned with current literature [29]. In a recent phase 3 randomized trial the usefulness of the mRNA-1273 vaccine was pointed up showing 94.1% efficacy at preventing COVID-19 disease, both asymptomatic and severe one [30].

At the time of writing, the fourth wave of COVID-19, sustained by the very high transmission rate of the B.1.1.529 (omicron) variant, is underway in Italy. Twenty-eight patients, after a median time of 3.5 months (range 0.5–4.7 months) from the third vaccine dose, experienced asymptomatic breakthrough infections. Despite the rapidly growing number of COVID-19 cases

in our country, this preliminary observation suggests that full vaccination should be recommended for cancer patients.

The study we presented has some limitations. First, our evaluation lacks of a control group of vaccinated patients without a diagnosis of cancer and screened for COVID-19 infection. Secondly, this study did not provide data regarding the antibody levels against the SARS-CoV-2 spike protein. This additional information may provide a more accurate indication about the efficacy of protection [31]. Indeed, in a prospective, single-center cohort study up to 6% of patients with solid tumors undergoing cancer treatment, mainly with poorer performance status, fail to obtain seroconversion after primary SARS-CoV-2 mRNA vaccination as compared with 0.2% of controls without cancer, accounting for a 30-fold higher probability [32]. After the third dose an additional, although incomplete, efficacy of vaccination in this population was reported, with an estimate of 35.7% of seroconversion probability [33]. On the other hand, the presence of neutralizing antibodies does not necessarily prove a mechanistic role in mediating protection, due to the possible action of other immune responses leading an apparent association.

The analysis we presented is further real world evidence about tolerance and efficacy of the mRNA vaccines in cancer patients. Our results can be put beside to others similar published experiences about this topic. The sum of all these efforts leads in one way: vaccination must be strongly recommended in patients with cancer, as it is safe and will reduce the risk or severity of COVID-19 illness. Cancer patients, caregivers, healthcare professionals, and more broadly, the general population should comply with public health measures to better protect vulnerable people from COVID-19 infection.

Author contributions

Maria Simona Pino: Conceptualization, Methodology, Formal analysis, Investigation, Resources, Data curation, Writing original draft, Supervision, Project administration. **Simone Cheli**: Methodology, Software, Validation, Formal analysis. **Marco Perna**: Investigation, Data Curation, Writing original draft. **Valentina Fabbroni**: Investigation, Resources, Data Curation, Writing Review & Editing. **Clara Giordano**: Investigation, Resources, Data Curation, Writing Review & Editing. **Francesca Martella**: Writing Review & Editing. **Fabio Lanini**: Writing Review & Editing. **Angela Stefania Ribecco**: Writing Review & Editing. **Silvia Scoccianti**: Investigation, Resources, Writing Review & Editing. **Carlotta Bacci**: Investigation, Resources, Writing Review & Editing. **Valentina Baldazzi**: Investigation, Resources, Writing Review & Editing. **Ilaria Bertolini**: Investigation, Resources, Writing Review & Editing. **Greta Di Leonardo**: Investigation, Resources, Writing Review & Editing. **Chiara Fulignati**: Investigation, Resources, Writing Review & Editing. **Raffaella Grifoni**: Investigation, Resources, Writing Review & Editing. **Elena Molinara**: Writing Review & Editing. **Sheila Rangan**: Investigation, Resources, Writing Review & Editing. **Renato Tassi**: Investigation, Resources, Writing Review & Editing. **Federica Furlan**: Writing Review & Editing. **Gil Goldzweig**: Methodology. **Andrea Bassetti**: Writing Review & Editing. **Luisa Fioretto**: Supervision, Writing Review & Editing.

Funding

No funding to be reported.

Conflict of interest statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

Acknowledgments

We thank Giada Bazzani (supported by C.A.L.C.I.T. Valdarno Fiorentino) for direct technical assistance.

References

[1] Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. Lancet Infect Dis 2020;20:533–4.
[2] Ministero della Salute; Presidenza del Consiglio dei Ministri; Istituto Superiore di Sanità; Agenzia Nazionale per i Servizi Sanitari Regionali; Agenzia Italiana del Farmaco. Vaccinazione anti-SARS-CoV-2/COVID-19. Piano strategico. Available online: http://www.salute.gov.it/imgs/C_17_pubblicazioni_2986_allegato.pdf (accessed on 20 January 2021). .
[3] Ribas A, Sengupta R, Locke T, et al. Priority Covid-19 vaccination for patients with cancer while vaccine supply is limited. Cancer Discov 2021;11:233–6.
[4] Kuderer NM, Choueiri TK, Shah DP, et al. Clinical impact of COVID-19 on patients with cancer (CCC19): a cohort study. Lancet 2020;395:1907–18.
[5] Williamson EJ, Walker AJ, Bhaskaran K, et al. Factors associated with COVID-19-related death using OpenSAFELY. Nature 2020;584:430–6.
[6] Elkrief A, Desilets A, Papneja N, et al. High mortality among hospital-acquired COVID-19 infection in patients with cancer: a multicentre observational cohort study. Eur J Cancer 2020;139:181–7.
[7] Lièvre A, Turpin A, Ray-Coquard I, et al. Risk factors for Coronavirus Disease 2019 (COVID-19) severity and mortality among solid cancer patients and impact of the disease on anticancer treatment: a French nationwide cohort study (GCO-002 CACOVID-19). Eur J Cancer 2020;141:62–81.
[8] de Joode K, Dumoulin DW, Tol J, et al. Dutch Oncology COVID-19 consortium: outcome of COVID-19 in patients with

cancer in a nationwide cohort study. Eur J Cancer 2020;141:171–84.
[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. European Journal of Cancer 2020;139:43–50.
[10] Yekedüz E, Utkan G, Ürün Y. A systematic review and meta-analysis: the effect of active cancer treatment on severity of COVID-19. Eur J Cancer 2020;141:92–104.
[11] Garassino MC, Whisenant JG, Huang LC, et al. COVID-19 in patients with thoracic malignancies (TERAVOLT): first results of an international, registry-based, cohort study. Lancet Oncol 2020;21:914–22.
[12] Aznab M, Eskandari Roozbahani N, Moazen H. Value of influenza vaccines in cancer patients during the coronavirus (COVID-19) pandemic: a cross-sectional study. Support Care Cancer 2021. https://doi.org/10.1007/s00520-021-06204-x.
[13] Bersanelli M, Buti S, Banna GL, et al. Impact of influenza syndrome and flu vaccine on survival of cancer patients during immunotherapy in the INVIDIa study. Immunotherapy 2020;12:151–9.
[14] COVID-19 vaccination in cancer patients: ESMO statements. Available at: https://www.esmo.org/covid-19-and-cancer/covid-19-vaccination. Accessed September 02, 2021.
[15] Documento AIOM CIPOMO COMU. Vaccinazione COVID-19 per I pazienti oncologici. .
[16] COVID-19 vaccines & patients with cancer. 09/03/2021.
[17] Waissengrin B, Agbarya A, Safadi E, Padova H, Wolf I. Short-term safety of the BNT162b2 mRNA COVID-19 vaccine in patients with cancer treated with immune checkpoint inhibitors. Lancet Oncol 2021;22:581–3.
[18] Goshen-Lago T, Waldhorn I, Holland R, et al. Serologic status and toxic effects of the SARS-CoV-2 BNT162b2 vaccine in patients undergoing treatment for cancer. JAMA Oncol 2021. https://doi.org/10.1001/jamaoncol.2021.2675.
[19] 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;22:765–78.
[20] Scoccianti S, Delli Paoli C, Grilli Leonulli B, et al. Acute tolerance of Moderna mRNA-1273 vaccine against COVID-19 in patients with cancer treated with radiotherapy. Lancet Oncol 2021;22. https://doi.org/10.1016/S1470-2045(21)00427-7.
[21] Venkatesulu BP, Chandrasekar VT, Girdhar P, et al. A systematic review and meta-analysis of cancer patients affected by a novel coronavirus. JNCI Cancer Spectr 2021;5. https://doi.org/10.1093/jncics/pkaa102.
[22] Giannakoulis VG, Papoutsi E, Siempos II. Effect of cancer on clinical outcomes of patients with COVID-19: a meta-analysis of patient data. 2020.
[23] Parere della Commissione tecnico-scientifica dell'AIFA in merito alla somministrazione di dosi aggiuntive di vaccini contro il SARS-CoV2/COVID-19 (9 settembre 2021). https://www.aifa.gov.it/documents/20142/1289678/Parere_CTS_09.09.2021.pdf.
[24] Food and Drug Administration. Toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials: guidance for industry. Food and Drug Administration; 2007 [September].
[25] di Noia V, Renna D, Barberi V, et al. The first report on coronavirus disease 2019 (COVID-19) vaccine refusal by patients with solid cancer in Italy: early data from a single-institute survey. Eur J Cancer 2021:153. https://doi.org/10.1016/j.ejca.2021.05.006.
[26] Barrière J, Gal J, Hoch B, et al. Acceptance of SARS-CoV-2 vaccination among French patients with cancer: a cross-sectional survey. Ann Oncol 2021;32. https://doi.org/10.1016/j.annonc.2021.01.066.
[27] Villarreal-Garza C, Vaca-Cartagena BF, Becerril-Gaitan A, et al. Attitudes and factors associated with COVID-19 vaccine hesitancy among patients with breast cancer. JAMA Oncol 2021;7. https://doi.org/10.1001/jamaoncol.2021.1962.
[28] 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 Dec 15;27(24):6815–23.
[29] Tran S, Truong TH, Narendran A. Evaluation of COVID-19 vaccine response in patients with cancer: an interim analysis. Eur J Cancer 2021;159:259–74. https://doi.org/10.1016/j.ejca.2021.10.013.
[30] 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(5):403–16. https://doi.org/10.1056/NEJMoa2035389.
[31] Ds, Cromer D, Reynaldi A, et al. Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. Nat Med 2021;27(7):1205–11. https://doi.org/10.1038/s41591-021-01377-8.
[32] 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 Mar;163:16–25.
[33] Patelli G, Pani A, Amatu A, et al. Seroconversion after SARS-CoV-2 mRNA booster vaccine in cancer patients. Eur J Cancer 2022 Mar;163:16–25.