# Immune-Related Adverse Events Among COVID-19–Vaccinated Patients With Cancer Receiving Immune Checkpoint Blockade

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## ABSTRACT

**Background:** Whether COVID-19 vaccination and the associated immune response increases susceptibility to immune-related adverse events (irAEs) among patients treated with immune checkpoint inhibition (ICI) remains unknown. Short-term follow-up can assess the safety of concurrent administration of the vaccine and ICI treatment. **Methods:** We conducted an electronic health record analysis of a cohort of 408 patients with cancer receiving ICI therapy and who were vaccinated for COVID-19 between January 16 and March 27, 2021. Patients were seen in follow-up for 90 days from the day of the first dose in this single-institution tertiary care center. We evaluated the incidence of irAEs and the frequency of each event type and grade among patients who experienced an irAE. We also evaluated the incidence of irAEs in patients who began a new immunotherapy agent after vaccination. **Results:** Among 408 patients with cancer receiving ICI therapy (median age, 71 years; 217 [53%] male), administration of a COVID-19 mRNA vaccine within 90 days of ICI treatment was not associated with an increased incidence of irAEs. A total of 27 (7%) patients experienced a new irAE within the observation period. Among patients with previous irAEs from ICIs (n=54), 3 (6%) experienced a recurrent irAE, and of those initiating a new immunotherapy (n=52), 9 (17%) experienced an irAE. No excess risk of COVID-19 diagnosis was seen in this subset of patients receiving ICI therapy, and no breakthrough COVID-19 cases were seen after full COVID-19 vaccination. **Conclusions:** These findings should reassure providers that COVID-19 vaccination during ICI therapy is safe and efficacious.

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## Background

Recently introduced vaccines for COVID-19 are a critical advance against the COVID-19 pandemic.[1,2] The postvaccine reduction in COVID-19–related hospitalization heralds the immense promise of these tools to reduce the impact of the COVID-19 pandemic among those at most significant risk, including patients with cancer.[3]

Active cancer treatment predisposes individuals to severe COVID-19 disease, and subdued vaccine immune responses are expected with certain cancer treatments. Among cancer therapies, immune checkpoint inhibition (ICI) has a negligible effect on vaccine-elicited immune responses.[4] For example, influenza vaccine studies demonstrate comparable immunogenicity in ICI-treated patients and healthy individuals, and validate the overall safety of immunization.[4] Still, with higher rates of immediate postvaccine adverse reactions with mRNA vaccines,[5] concerns have emerged about the risk for immune-related adverse events (irAEs) after COVID-19 immunization. In addition, patients receiving active cancer treatment were excluded from key COVID-19 vaccine trials.[1,2] Therefore, establishing the safety and efficacy of mRNA vaccines in patients receiving ICI therapy by extended monitoring for postvaccine irAEs is critical. This study characterizes irAEs and COVID-19 incidence in patients who received an mRNA vaccine within 90 days of ICI treatment.

## Methods

The study institution, Memorial Sloan Kettering Cancer Center (MSKCC), is a 574-bed tertiary care cancer center in New York City. MSKCC began vaccinating patients with the 2 severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mRNA vaccines on January 16, 2021, according to a priority scheme developed by New York State. Electronic pharmacy records were used to identify all patients vaccinated with a first dose between January 16 and March 27, 2021, and who received FDA-approved ipilimumab, pembrolizumab, or nivolumab within 90 days before or after their first vaccination dose. Clinicopathologic parameters related to any-grade new-onset irAEs occurring after the first vaccine dose and ICI initiation, as

defined by the CTCAE version 4.0, were collected, along with data on vaccine manufacturer, age at vaccination, sex, tumor type, dates and type(s) of ICI administration, and death during the follow-up period.

We determined the incidence of irAEs in patients who received immunotherapy within 90 days before or after the first dose of an mRNA SARS-CoV-2 vaccine, following up patients for 90 days from the day of vaccination. For patients who experienced an irAE during the follow-up period, we summarized the frequency of each event type and grade. In bivariate analyses (chi-square test, Fisher exact test, Wilcoxon rank-sum test), we compared patients who did versus did not experience an irAE during the follow-up period with respect to age, sex, tumor type, previous irAE, previous SARS-CoV-2 infection, vaccine type, immunotherapy type, proximity of date of immunotherapy administration to vaccination date, initiation of new immunotherapy after vaccination, death during follow-up, and total days of follow-up observed. We also calculated the incidence rate of irAEs in patients who began a new immunotherapy agent after vaccination. The MSKCC Institutional Review Board granted a HIPAA waiver of authorization to conduct this study.

## Results

A total of 408 patients received a first dose of SARS-CoV-2 mRNA vaccine within 90 days before or after treatment with an ICI agent. Patients ranged in age from 55 to 93 years (median, 71 years), and the cohort was 53% male (n=217). Patients were receiving treatment for thoracic cancer (n=122; 30%), genitourinary cancer (n=84; 21%), upper gastrointestinal cancer (n=50; 12%), melanoma (n=47; 12%), gynecologic cancer (n=41; 10%), sarcoma (n=20; 5%), head and neck cancer (n=19; 5%), lower gastrointestinal cancer (n=13; 3%), glioblastoma (n=5; 1%), lymphoma (n=4; 1%), and breast cancer (n=3; 1%). Within the 90-day windows before and after the first vaccine dose, patients were treated with pembrolizumab only (n=264; 65%), nivolumab only (n=99; 24%), combination ipilimumab + nivolumab (n=41; 10%), ipilimumab only (n=3; 0.7%), or all 3 agents (n=1; 0.3%). Most patients (95%; n=389) received the Pfizer-BioNTech vaccine.

A total of 27 (7%) patients experienced a new irAE during the follow-up period. Among patients with a history of irAEs before vaccination (n=54), 3 (6%) experienced an irAE during the postvaccination follow-up period. Most new irAEs were mild (grade 1, n=21; 78%) (Table 1). All 4 patients who experienced a severe (grade 3) irAE had gastrointestinal events (colitis or diarrhea). Three of these patients were treated with combination ipilimumab + nivolumab, and one was treated with single-agent pembrolizumab. No patients experienced a flare of a prior irAE after vaccination. Table 2 compares characteristics of patients who did versus did not experience an irAE. No significant differences in baseline characteristics or treatment were seen between these groups, except that patients beginning a new immunotherapy agent during the follow-up period were more likely to experience an irAE. Of 28 patients who received the first vaccine dose and ICI therapy on the same day, none developed an irAE during the follow-up period. Among patients who began a new immunotherapy agent after vaccination (n=52), 17% developed an irAE (n=9; incidence rate, 2.7 per 1,000 patient-days observed). Median follow-up after initiation of the new immunotherapy agent in these patients was 78.5 days (range, 33–88 days). Figure 1 presents a swimmer's plot describing the treatment history and trajectory of patients who experienced an irAE during the follow-up period.

**Table 1. irAEs Following SARS-CoV-2 mRNA Vaccine and ICI Therapy**

| irAE | Grade 1 | Grade 2 | Grade 3 |
|---|---|---|---|
| Arthralgias | 3 | — | — |
| Arthritis + rash | 1 | 1 | — |
| Colitis | — | — | 1[a] |
| Dermatitis | 10 | — | — |
| Diarrhea | 2 | — | 3[b] |
| Pneumonitis | 2 | 1 | — |
| Thyroiditis | 1 | — | — |
| Transaminitis | 2 | — | — |
| **Total** | **21** | **2** | **4** |

Abbreviations: ICI, immune checkpoint inhibitor; irAE, immune-related adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
[a]Patient treated with single-agent pembrolizumab.
[b]Patients treated with combination ipilimumab + nivolumab.

Two patients in our cohort developed COVID-19 infection after vaccination (through August 31, 2021). In patients with previous COVID-19 infection (n=11), the median duration to COVID-19 vaccination and ICI therapy was 4 months.

## Discussion

The overall incidence of irAEs was 7% in our cohort of 408 ICI-treated patients who received the COVID-19 vaccine. In 52 patients who began a first ICI therapy after vaccination, the incidence of irAEs (17%) is similar to published reports.[6,7] For example, a recent study of pembrolizumab as adjuvant therapy in 509 patients with resected stage III melanoma found an irAE incidence of 19% within 3 months of treatment initiation[6]; most irAEs were mild. No differences were observed in the risk of irAEs in those with and without preexisting immune toxicities. Furthermore, our cohort included 11 individuals with prior COVID-19 infection, and severe immediate reactogenicity from the vaccine or irAEs was not observed in any of them.

ICI is a standard treatment option for many cancers. In contrast to conventional chemotherapy, vaccine responses

**Table 2. Patient Characteristics After Receipt of SARS-CoV-2 mRNA Vaccine and ICI Therapy**

| Characteristic | Patients Who Experienced irAEs n (%) | Patients Who Did Not Experience irAEs n (%) | *P* Value |
|---|---|---|---|
| Total, n | 27 | 381 | |
| Sex | | | .35 |
| Male | 12 (6) | 205 (94) | |
| Female | 15 (9) | 176 (91) | |
| Age, median (IQR), y | 75 (66–78) | 71 (66–78) | .76 |
| Tumor type | | | [a] |
| Breast | 2 (67) | 1 (33) | |
| Gastrointestinal, lower | 0 (0) | 13 (100) | |
| Gastrointestinal, upper | 4 (8) | 46 (92) | |
| Genitourinary | 6 (7) | 78 (93) | |
| Glioblastoma | 0 (0) | 5 (100) | |
| Gynecologic | 4 (10) | 37 (90) | |
| Head and neck | 2 (11) | 17 (89) | |
| Lymphoma | 1 (25) | 3 (75) | |
| Melanoma | 3 (6) | 44 (94) | |
| Sarcoma | 1 (5) | 19 (95) | |
| Thoracic | 4 (3) | 118 (97) | |
| Previous infection with SARS-CoV-2 | 0 (0) | 11 (100) | .99 |
| Previous irAE | 3 (6) | 51 (94) | .99 |
| Received Pfizer-BioNTech vaccine | 27 (7) | 362 (93) | .24 |
| Received nivolumab[b] | 11 (8) | 130 (92) | .48 |
| Received pembrolizumab[b] | 16 (6) | 249 (94) | .52 |
| Received ipilimumab[b] | 5 (11) | 40 (89) | .20 |
| Died during follow-up | 0 (0) | 18 (100) | .62 |
| Receipt of vaccine first dose and immunotherapy within same week | 8 (4) | 189 (96) | .04 |
| Receipt of vaccine second dose and immunotherapy within same week (date imputed) | 1 (4) | 22 (96) | .99 |
| Started new immunotherapy agent during follow-up period | 9 (17) | 43 (83) | <.001 |
| Days observed, median (IQR) | 90 (71–90) | 90 (90–90) | .01 |

Abbreviations: ICI, immune checkpoint inhibitor; IQR, interquartile range; irAE, immune-related adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
[a]*P* value not reported due to cell sizes <5.
[b]Data include receipt by any agent.

are not significantly impaired in patients treated with ICIs. Influenza vaccine studies report a high serologic response rate among ICI recipients without an exaggerated risk of irAEs.[4,7] Similarly, emerging studies in mRNA-vaccinated patients with cancer show high antibody levels among ICI-treated individuals that are comparable to levels among healthy control subjects and superior to humoral responses in chemotherapy recipients.[8,9]

Despite proven efficacy in larger populations, there are substantial lingering concerns regarding the long-term safety of vaccines in ICI-treated patients. Early experience from Israel in patients receiving ICI treatment found that 19% were vaccine-reluctant due to toxicity concerns. This report examined the short-term safety of ICI with the vaccine in 134 patients and over a brief median follow-up period of 19 days after vaccination.[5] They did not observe higher immediate adverse events, risk of new irAEs, or exacerbation of preexisting irAEs. Similarly, in a study of 81 ICI-treated patients in whom vaccine and immunotherapy were administered within 30 days,[10] no

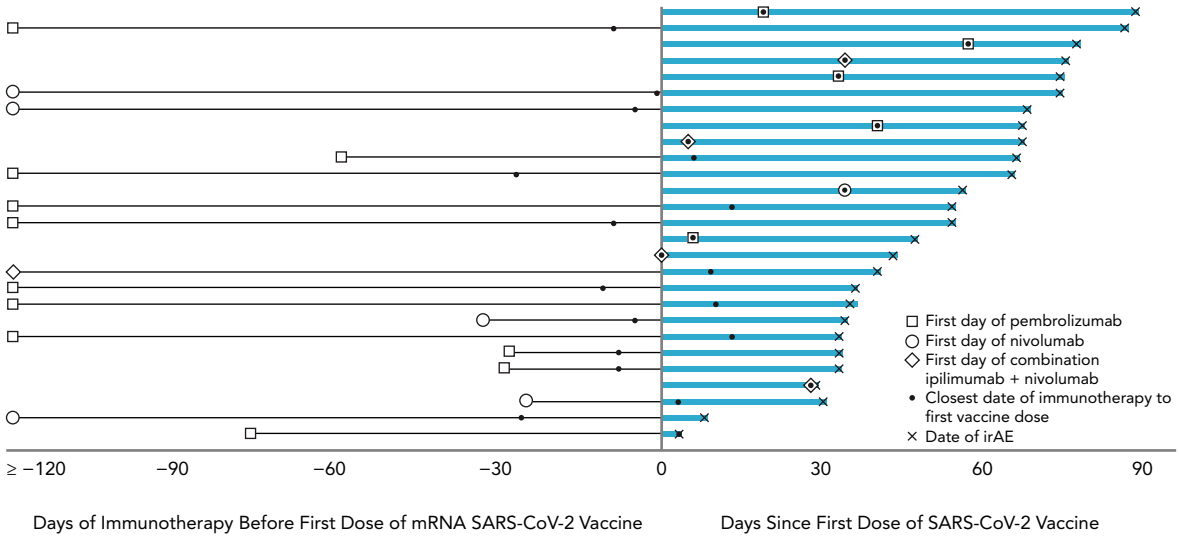


**Figure 1.** Swimmer's plot depicting days from first dose of mRNA SARS-CoV-2 vaccine to irAEs among patients who received an ICI within 90 days before or after vaccination and experienced an irAE after receipt of immunotherapy and vaccine (n=27).
Abbreviations: ICI, immune checkpoint inhibitor; irAE, immune-related adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

patients experienced new adverse events. Our findings add a sizable number of newly treated patients and a longer follow-up period to capture irAEs.

We note that any conclusions about comparative incidence must be interpreted with caution, given biases implicit within cross-trial comparisons. An important limitation of our study is the absence of a temporally aligned comparison group of patients at our center receiving ICI therapy who did not receive the COVID-19 vaccine. We further note that the sample size of our study is not appropriately powered to capture the risk of postvaccine rare events such as Guillain-Barré syndrome and others.

## Conclusions

Our data do not show a higher risk of immune toxicity among ICI-treated patients who received the COVID-19 vaccine, including those newly started on therapy. The findings should encourage new and third-dose vaccine uptake among patients with cancer receiving ICI treatment, without interruption of cancer therapy.

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