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RESEARCH ARTICLE

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Safety of COVID-19 vaccines in subjects with solid tumor cancers receiving immune checkpoint inhibitors

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ABSTRACT

The incidence of severe immune-related adverse events (irAEs) in cancer subjects receiving immune checkpoint inhibitors (ICIs) following COVID-19 vaccination and the relationship between the incidence of severe irAE and the interval between COVID-19 vaccination and ICI dose have not been established. We performed a retrospective study evaluating the incidence of irAEs in solid tumor subjects receiving ICI therapy who received any COVID-19 vaccinations since FDA authorization. irAEs were defined as severe with one or more grade 3 or above events (CTCAE v5.0), multiple organ involvement, or requiring hospitalization for management. Two hundred and eighty-four subjects who received COVID vaccinations from December 2020 and February 2022 were included in this analysis [median age at vaccination 67 years (IQR 59.0–75.0); 67.3% male]. Twenty-nine subjects (10.2%) developed severe irAEs, of which 12 subjects (41.4%) received ICI monotherapy, 10 subjects (34.5%) received combination ICI therapy with nivolumab and ipilimumab, and 7 subjects (24.1%) received ICI plus VEGFR-TKI therapy. Hospitalization occurred in 62% of subjects with severe irAEs, with a median duration of 3 days (IQR: 3.0–7.5 days). Immunosuppressive therapy was required in 79.3%, with a median duration of 103 days (IQR: 42.0–179.0). ICI therapy was discontinued in 51.7% of subjects with severe irAE; dosing was held or interrupted in 34.5%. Among severe irAEs, the median interval between vaccination and ICI treatment closest to the occurrence of severe irAE was 15.5 days (IQR: 10.0–23.0). In solid tumor cancer subjects receiving ICIs, COVID-19 vaccination is not associated with an increased incidence of severe irAEs compared to historical data and may be safely administered during ICI cancer therapy in subjects who lack contraindications.

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Introduction

The COVID-19 pandemic has presented numerous disruptions for cancer subjects, including delays in diagnosis and treatment.[1] In addition, cancer subjects may have up to a five-fold increased mortality risk with COVID-19 infection.[2,3] Due to the number of COVID-19-related concerns in cancer subjects, when three vaccines were granted Emergency Use Authorization (Pfizer Bio-N- Tech, Moderna, and Johnson and Johnson), cancer subjects were prioritized in CDC distribution guidelines.[4] In addition, oncology professional organizations, including ASCO, ESMO, and NCCN, have endorsed vaccination for all eligible persons, including both cancer subjects undergoing treatment and cancer survivors 6 months of age and older, based on FDA-approved indications or emergency use authorization (EUA).[5–7] Cancer subjects may also be more willing than the public to be vaccinated against COVID-19.[8]

The first immune checkpoint inhibitor (ICI), ipilimumab, was approved for metastatic melanoma in 2011. Since then, six additional ICIs have been approved for numerous other cancer indications. Subsequently, the estimated proportion of cancer subjects eligible to receive immunotherapy increased from 1.54% in 2011 to 43.63% in 2020.[9] With the introduction and expansion of ICI therapy for the adjuvant and metastatic treatment of malignancies, the profile of adverse events in subjects receiving anti-cancer therapy has also markedly changed. Immune-related adverse events (irAEs) include autoimmune toxicities in many organ systems, with varying severity from mild to life-threatening.[10]

There has been a concern that concurrent infection with COVID-19 while receiving ICIs may worsen irAE, and the adequacy of antibody response to vaccination against COVID-19 in subjects receiving ICIs may be altered.[11] subjects with cancer receiving ICIs have been found to have likely adequate cell-mediated immune responses to the influenza vaccine.[12] A pooled analysis of 21 studies with over 5000 cancer subjects found that serological response to COVID-19 vaccine was weaker and more heterogeneous in subjects with cancer compared to healthy controls, the serologic response was higher with second dose of vaccine, and seroconversion in subjects with hematological malignancies was significantly lower than that in subjects with solid tumors.[13]

Studies evaluating the short-term safety of COVID-19 vaccines in subjects receiving anti-cancer therapy have generally shown the vaccines to be safe and tolerable in terms of local

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and systemic effect.[14–16] For example, one prospective observational study found that subjects with cancer developed poorer immune responses to the first dose of the Pfizer – BioNTech BNT162b2 vaccine than healthy controls. However, immunogenicity in subjects with cancer increased significantly in the two weeks following the second dose of BNT162b2. Additionally, this study found that the vaccine was overall well-tolerated, with 54% of subjects reporting no toxicities following their first dose and 71% following their second. The most common reaction reported was injection site pain within the 7 days following administration (35%).[14] One potential confounder in administering the COVID-19 vaccine to cancer subjects receiving ICI therapy is the regional lymphadenopathy that can develop after vaccination, which can, in some cases, confound the interpretation of cancer response.[15,17]

The American Society of Clinical Oncology recommends strategies such as providing the vaccine in between cycles of therapy and after appropriate waiting periods for subjects receiving stem cell transplants and immune globulin treatment to reduce the risks while maintaining the efficacy of vaccination.[5] The incidence of severe immune-related side effects in subjects receiving ICIs following COVID-19 vaccination and the relationship between incidence of severe irAEs and the time interval between COVID-19 vaccination and ICI dose has not been established.

In this retrospective chart review, we aim to evaluate the incidence severe ICI-immune-related adverse events in subjects with solid tumors who have concurrent COVID-19 vaccination and ICI cancer therapy.

Materials and methods

Study design, eligibility, and procedures

This study was an IRB-approved, institutional, retrospective cohort study evaluating cancer subjects who received treatment with any of the FDA-approved immune checkpoint inhibitors and at least one dose of COVID-19 vaccine. subjects were grouped into cohorts by cancer type including melanoma, renal cell carcinoma (RCC), urothelial/bladder carcinoma, hepatocellular cancer (HCC), gynecologic cancers, squamous cell carcinoma of the head and neck (H&N), and squamous cell carcinoma of the skin (SCC). subjects were eligible if they received at least one dose of FDA-authorized vaccination against COVID-19 and at least one treatment with an immune-checkpoint inhibitor, either as monotherapy or in combination. subjects were identified using the University of Colorado/UCHealth electronic medical record database search including pharmacy records.

Data collection

Information was obtained from review of electronic medical records. Data collected included baseline demographics, cancer treatment history, COVID-19 vaccination history, and the occurrence of severe immune-related events and their sequelae. Immune-related events were defined as severe if they satisfied one or more of the following criteria: grade 3 or above as designated by the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0,[18] multiple organ involvement or requiring hospitalization for management. Severe irAEs were included in the analysis if they were not present prior to vaccination or if their baseline status worsened to meet the criteria for a severe irAE following immunization.

End points

The primary end point of this study was the incidence of severe immune-related adverse events in subjects who received treatment with an ICI within 90 days of vaccination. The secondary end points included requirement for and duration of immunosuppressive therapy in subjects who experienced a severe irAE, median time between vaccination and ICI treatment in subjects who experienced a severe irAE, and discontinuation rate following severe irAE.

Statistical analysis

Descriptive statistics are presented for baseline characteristics of the entire subject population and by cohort. For categorical variables, the frequencies and percentage were calculated. For continuous variables, the median and interquartile range (IQR) were reported. In addition, the frequency of the incidence, estimated percentage and the 95% exact confidence interval were reported for the severe irAE for all subjects and by cohort. All statistical analyses were performed by an independent statistician to ensure unbiased data review. Statistical analyses were conducted on R version 4.1.0.[19]

Results

Participant demographic and clinical characteristics

Two hundred eighty-four subjects who received COVID vaccinations from December 2020 and February 2022 were included (Table 1). The median age at the time of first COVID-19 vaccination was 67 years (IQR 59.0–75.0); 67.3% of participants were male. Most subjects were treated with ICI monotherapy (70.8%), 18.7% were treated with combination ICI–ICI therapy, and 10.5% were treated with the combination of ICI plus an additional agent including chemotherapy, a tyrosine kinase inhibitor, or monoclonal antibody. The most common cancer types were melanoma (41.5%, 118 subjects), renal cell carcinoma (RCC, 20.4%, 58 subjects), and bladder cancers (14.1%, 40 subjects). The Pfizer Bio-N-Tech vaccine was received by 55.6% subjects, Moderna vaccine by 42.3% subjects, and Johnson and Johnson vaccine by 2.1% subjects. At the time of data cutoff, most subjects (74.6%) received three or more COVID-19 vaccine doses; 21.1% received two doses, and 3.9% received one dose.

Treatment to vaccination interval

In 35.9% of all subjects, the interval between ICI and SARS-CoV-2 vaccine was<7 days. 51.7% of severe irAEs occurred after the second vaccine dose, and 31% occurred after the third dose. Among all subjects who experienced severe irAEs,

Table 1. Baseline characteristics for all subjects.

Characteristic		SirAE: Yes (*N* = 29)	SirAE: No (*N* = 255)	Total (*N* = 284)
Age at first COVID vaccination	Median (IQR)	66.5 (56.2 to 71.0)	67.0 (59.8 to 75.0)	67.0 (59.0 to 75.0)
Gender	Male	19 (65.5)	172 (67.5)	191 (67.3)
	Female	10 (34.5)	83 (32.5)	93 (32.7)
Race	White	26 (89.7)	237 (92.9)	263 (92.6)
	Black	1 (3.4)	5 (2.0)	6 (2.1)
	Asian	2 (6.9)	2 (0.8)	4 (1.4)
	Other	0 (0.0)	11 (4.3)	11 (3.9)
Ethnicity	Hispanic	2 (6.9)	17 (6.7)	19 (6.7)
	Non-Hispanic	27 (93.1)	238 (93.3)	265 (93.3)
ICI therapy type	Monotherapy	12 (41.4)	189 (74.1)	201 (70.8)
	Combo ICI-ICI	10 (34.5)	43 (16.9)	53 (18.7)
	Combo ICI-Other	7 (24.1)	23(9.0)	30 (10.5)
Manufacturer of vaccination received	Pfizer	16 (55.2)	142 (55.7)	158 (55.6)
	Moderna	12 (41.4)	108 (42.3)	120 (42.3)
	Johnson and Johnson	1 (3.4)	5 (2.0)	6 (2.1)
Number of COVID-19 vaccinations received (10.2)	1	1 (3.4)	10 (3.9)	11 (3.9)
	2	8 (27.6)	52 (20.4)	60 (21.1)
	3	20 (69.0)	192 (75.3)	212 (74.6)
	(Missing)	0 (0.0)	1 (0.4)	1 (0.4)
Shortest interval between most recent ICI dose and vaccination	≥7 days	20 (69.0)	162 (63.5)	182 (64.1)
	<7 days	9 (31.0)	93 (36.5)	102 (35.9)
Cancer type	Bladder	6 (20.7)	34 (13.3)	40 (14.1)
	Gynecologic	0 (0.0)	15 (5.9)	15 (5.3)
	Head & Neck	0 (0.0)	15 (5.9)	15 (5.3)
	Hepatocellular carcinoma	1 (3.4)	18 (7.0)	19 (6.7)
	Melanoma	10 (34.5)	108 (42.4)	118 (41.5)
	Renal cell carcinoma	11 (37.9)	47 (18.4)	58 (20.4)
	Squamous cell carcinoma	1 (3.4)	18 (7.0)	19 (6.7)

SirAE = Severe immune-mediated adverse event.
ICI = Immune checkpoint inhibitor.
ICI-Other = ICI plus chemotherapy or vascular endothelial growth factor receptor tyrosine kinase inhibitor or monoclonal antibody.

the median interval between vaccination and ICI treatment closest to the occurrence of severe irAE was 15.5 days (IQR: 10.0–23.0). The breakdown of clinical characteristics by cancer cohort is presented in Table 2.

Incidence of severe immune-related adverse events

Severe irAEs occurred in 29 subjects (10.2%), including 11 subjects with RCC, 10 subjects with melanoma, 6 subjects with bladder cancer, and 1 subject each with hepatocellular carcinoma (HCC) and squamous cell carcinoma (SCC) (Table 3). Among subjects who experienced severe irAEs, 12 subjects (41.4%) received ICI monotherapy (1 RCC, 6 bladder, 3 melanoma, 1 HCC, 1 SCC), other 10 subjects (34.5%) received combination ICI therapy with nivolumab and ipilimumab (3 RCC and 7 melanoma), and 7 subjects received ICI plus VEGFR-TKI (all RCC). No severe irAEs were recorded in subjects with head and neck cancers or gynecologic cancers. Hospitalization was required for management of severe irAE in 62% of subjects with severe irAEs (Table 4) with a median length of stay of 3 days (IQR: 3.0–7.5 days). Immunosuppressive therapy (i.e., steroids) was required in 79.3% of subjects with severe irAEs, with a median immunosuppressive therapy duration of 103 days (IQR: 42.0–179.0). ICI therapy was discontinued in over 51.7% subjects who experienced severe irAE and ICI dosing was held or interrupted in another 34.5% subjects.

Discussion

Our retrospective study reported the incidence of severe immune-related adverse events in cancer subjects receiving immune checkpoint inhibitor therapy and who were vaccinated against Sars-CoV-2. We found that severe irAE occurred in 29 of 284 subjects on ICI therapy (10.2%), "most commonly in subjects with melanoma, RCC, and bladder cancer as these subjects made up most subjects in this study. The rates of severe irAE varied among the various cancer cohorts (0% in H&N and gynecologic, 5.3% in HCC and SCC, 8.5% in melanoma, 15% in bladder, and 19% in RCC cohorts), most likely reflecting the higher number of subjects, use of combination ICI therapy, and more prolonged ICI exposure as standard of care in the later cohorts. The rates of hospitalization and need and duration of immunosuppressive therapy for treatment of severe irAEs are similar to those seen in routine clinical practice.

The incidence of severe irAE in our study is lower than previously reported incidence of G3 and higher AEs with the combination of nivolumab and ipilimumab (18% in melanoma subjects, 46% in RCC subjects), pembrolizumab monotherapy (10.1%–13.3% in melanoma subjects, 15% in bladder cancer subjects), and nivolumab monotherapy (18% in bladder cancer subjects, 19% in RCC subjects, and 14–22% in melanoma subjects).[20–29]

A recent retrospective study of 408 cancer subjects by Widman and colleagues similarly reported that administration of a COVID-19 mRNA vaccine within 90 days of ICI treatment was not associated with an increased incidence of irAEs (6% of

Table 2. subject characteristics by cancer cohort.

		RCC	Melanoma	Bladder	HCC	SCC	Gyn	H&N	Total
Number of subjects		58	118	40	19	19	15	15	284
Age at first COVID vaccination (years)	Median (IQR)	65.0 (56.2–71.5)	64.5 (54.2–71.8)	72.5 (66.0–79.2)	70.0 (63.5–74.0)	77.0 (72.0–82.5)	67.0 (64.5 to 75.0)	66.0 (61.5–72.0)	67.0 (59.0 to 75.0)
ICI therapy type	Monotherapy	26 (44.8)	85 (72.0)	37 (92.5)	9 (47.4)	19 (100.0)	10 (66.7)	15 (100.0)	201 (70.8)
	Combo ICI-ICI	9 (15.5)	31 (26.3)	2 (5.0)	10 (52.6)	0	1 (6.7)	0	53 (18.7)
	Combo ICI-Other	23 (39.7)	2 (1.7)	1 (2.5)	0	0	4 (26.7)	0	30 (10.5)
Number of COVID-19 vaccinations received	1	4 (6.9)	4 (3.4)	2 (5.0)	1 (5.3)	0	0	0	11 (3.9)
	2	16 (27.6)	11 (9.3)	11 (27.5)	8 (42.1)	5 (26.3)	6 (40.0)	3 (20.0)	60 (21.1)
	3	37 (63.8)	103 (87.3)	27 (67.5)	10 (52.6)	14 (73.7)	9 (60.0)	12 (80.0)	212 (74.6)
	Missing	1 (1.7)	0	0	0	0	0	0	1 (0.4)
Shortest interval between most recent ICI dose and vaccination	≥7 days	38 (65.5)	74 (62.7)	35 (87.5)	8 (42.1)	12 (63.2)	7 (46.7)	8 (53.3)	182 (64.1)
	<7 days	20 (34.5)	44 (37.3)	5 (12.5)	11 (57.9)	7 (36.8)	8 (53.3)	7 (46.7)	102 (35.9)

RCC = Renal cell carcinoma.
HCC = Hepatocellular carcinoma.
SCC = Squamous cell carcinoma (skin).
Gyn = Gynecological cancers.
H&N = Head and neck cancers.
irAE = Immune-mediated adverse effect.
ICI = Immune checkpoint inhibitor.
ICI-Other = ICI plus chemotherapy or vascular endothelial growth factor receptor tyrosine kinase inhibitor or monoclonal antibody.

Table 3. Incidence of severe irAE and estimated percentage of incidence with exact 95% confidence interval.

Cohort	Number of severe irAE	Number of subjects	Estimated percent of incidence	95% exact CI
All	29	284	10.2	(6.9, 14.3)
Bladder	6	40	15.0	(5.7, 29.8)
Gynecologic	0	15	0.0	(0, 21.8)
Head & Neck	0	15	0.0	(0, 21.8)
Hepatocellular carcinoma	1	19	5.3	(0.1, 26)
Melanoma	10	118	8.5	(4.1, 15)
Renal cell carcinoma	11	58	19.0	(9.9, 31.4)
Squamous cell carcinoma	1	19	5.3	(0.1, 26)

irAE = Immune-mediated adverse effect.
CI = Confidence interval.

subjects with previous irAEs experienced a recurrent irAE, and 17% of subjects initiating new immunotherapy experienced an irAE).[30]

Dzimitrowicz and colleagues found that among a cohort of 36 RCC subjects receiving ICI monotherapy or ICI-VEGFR TKI combination therapy compared to 36 RCC subjects not receiving cancer therapy, the ICI cohort had a higher rate of post-vaccination symptoms, but that the rate of new or worsening immune-related AEs was no higher than previously reported.[31]

Over 90% of cancer subjects in our study received two or more COVID-19 vaccinations, consistent with prior reports of higher willingness of cancer subjects to receive the SARS-CoV-2 vaccines. For example, a Dutch survey of 2412 subjects with cancer reported that 66% were willing to be vaccinated against COVID-19, 37% wanted to be prioritized for vaccination, and only 6% intended to refuse vaccination.[8] A Korean survey of 1001 cancer subjects showed that 61.8% of respondents were willing to receive the COVID-19 vaccine and that physician's recommendations effectively reduced subjects' vaccine hesitancy (91.2% of cancer subjects were willing to be vaccinated if their attending physicians recommend it).[32] We did not report on the overall rates of COVID-19 vaccination in all cancer subjects or all cancer subjects receiving ICI therapy at our institution, as this was beyond the scope of our retrospective study.

Interestingly, of the subjects who experienced severe irAE in our study, only five (17.2%) experienced a severe irAE after their first vaccine. In comparison, the majority occurred after their second vaccine (15 subjects, 51.7%) or third vaccine (9 subjects, 31.0%). Some experts have postulated that there may be a reciprocal interaction between COVID-19 vaccination and ICIs in that the vaccination could influence immunotherapy and that immunotherapy could impact COVID-19 vaccination.[33] The VOICE study ('vaccination against COVID-19 in cancer;' ClinicalTrials.gov identifier, NCT04715438) is a longitudinal, Dutch, multi-cohort study to evaluate immune response and adverse events after COVID-19 vaccination in subjects with solid malignancies undergoing immunotherapy, chemotherapy, or immunochemotherapy.[8] Recent studies evaluating the robustness of immune response to SARS-CoV-2 vaccination after ICI therapy in cancer subjects have shown that responses to SARS-

Table 4. irAE characteristics for subjects who experienced severe irAE.

		RCC	Melanoma	Bladder	HCC	SCC	Gyn	H&N	Total
Number of subjects		11	10	6	1	1	0	0	29
Time between vaccine dose and ICI dose closest to severe irAE (days)	Median (IQR)	11.0 (7.5–15.5)	19.5 (11.8–22.5)	22 (15.8–36.5)	121 (121.0–121.0)	8 (8.0–8.0)	NA	NA	15.5 (10.0 to 23.0)
Vaccine dose preceding SirAE	1	4 (36.4)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	NA	NA	5 (17.2)
	2	3 (27.3)	7 (70.0)	3 (50.0)	1 (100.0)	1 (100.0)	NA	NA	15 (51.7)
	3	4 (36.4)	3 (30.0)	2 (33.3)	0 (0.0)	0 (0.0)	NA	NA	9 (31.0)
Hospitalization for severe irAE	No. (%)	6 (54.5)	5 (50.0)	6 (100.0)	0	1 (100.0)	NA	NA	18 (62.0)
Length of hospitalization	Median (IQR)	6.5 (3.5–14.8)	5.0 (3.0–6.0)	3 (2.2–3.0)	NA	3 (3.0–3.0)	NA	NA	3.0 (3.0 to 7.5)
Requirement for immunosuppressive therapy	No. (%)	10 (90.9)	9 (90.0)	3 (50.0)	1 (100.0)	0	NA	NA	23 (79.3)
Duration of immunosuppressive therapy	Median (IQR)	85.5 (36.8–176.0)	128 (94.0–232.0)	64 (47.0–83.5)	20 (20.0–20.0)	0	NA	NA	103 days (42.0–179.0).
Discontinuation of ICI	Discontinued	6 (54.5)	3 (30.0)	5 (83.3)	0	1 (100.0)	NA	NA	15 (51.7)
	Resumed without interruption	0	3 (30.0)	1 (16.7)	0	0	NA	NA	4 (13.8)
	Held/dose interrupted	5 (45.5)	4 (40.0)	0	1 (100.0)	0	NA	NA	10 (34.5)

RCC = Renal cell carcinoma.
HCC = Hepatocellular carcinoma.
SCC = Squamous cell carcinoma (skin).
Gyn = Gynecological cancers.
H&N = Head and neck cancers.
irAE = Immune-mediated adverse effect.
ICI = Immune checkpoint inhibitor.

CoV-2 vaccinations may be reduced with certain groups (hematologic cancer subjects receiving anti-CD20 antibodies, solid tumor subjects on immunosuppressive chemotherapy) but were not diminished in other groups, including cancer subjects receiving ICI therapy.[34–39] A retrospective study of 84 subjects receiving ICI monotherapy by Chen and colleagues showed that after a minimum of 30 days of follow-up from the second dose of vaccine, zero of the 84 (95% CI, 0.0%–4.5%) subjects had exacerbation of previous irAEs or diagnosis of new irAEs.[40]

All the subjects in our retrospective study received either Pfizer Bio-N-Tech, Moderna, or Johnson and Johnson COVID-19 vaccines. In the absence of prospective controlled trials, our retrospective study adds to the current body of evidence, supporting the safety of these COVID-19 vaccines in subjects with cancer receiving ICIs. No subject received Astra Zeneca, Sinopharm, or other vaccines; therefore, we are not able to comment on the safety of these vaccines in the setting of immunotherapy. There are still many areas of uncertainty in the interactions between COVID-19 vaccines and checkpoint inhibitor immunotherapies; therefore, additional preclinical and clinical investigations are needed.

Conclusions

In solid tumor cancer subjects receiving ICI therapy, COVID-19 vaccination is not associated with increased incidence of severe irAEs compared to historical data. COVID-19 vaccines may be safely administered during ICI cancer therapy in subjects who do not have contraindications.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Prior presentations

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