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.

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Letter to the Editor

COVID-19 mRNA vaccines and immune-related adverse events in cancer patients treated with immune checkpoint inhibitors

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Dear Editor,

The Coronavirus Disease 2019 (COVID-19) messenger RNA (mRNA) vaccines, BNT162b2 and mRNA-1273, manufactured by Pfizer-BioNTech and Moderna, respectively, received the United States Food and Drug Administration (FDA) emergency use authorisation in December 2020 and have since been widely administered. Recognising the increased mortality risk from COVID-19 in cancer patients [1], the major cancer scientific societies such as the American Society of Clinical Oncology (ASCO) [2], European Society for Medical Oncology (ESMO) [3], and National Comprehensive Cancer Network (NCCN) [4] generally recommend COVID-19 vaccination in cancer patients if there are no contraindications. However, patients with active cancer were excluded from the landmark vaccine trials [5]. In addition, immune checkpoint inhibitors (ICIs) now constitute the contemporary standard-of-care systemic regimens across various cancer types. Therefore, there is a concern regarding the risk of immune-related adverse events (irAEs) after administration of COVID-19 mRNA vaccines in patients with cancer treated with an ICI, albeit there is a paucity of data.

To further investigate this essential topic in cancer care, we conducted a retrospective chart review using the electronic medical record at Vanderbilt University Medical Centre (VUMC). The study cohort included cancer patients who received ICIs within one month of receiving a COVID-19 mRNA vaccine. All patients received two doses of COVID-19 mRNA vaccine as recommended by the manufacturers and had at least 30 days of follow-up after the second dose of vaccine. The primary outcome was the rate of irAEs. Additionally, the United States Centres of Disease Control (CDC) and FDA's Vaccine Adverse Event Reporting System (VAERS) database was reviewed for reported possible irAEs after COVID-19 vaccine administration. This study was approved by the institutional review board at VUMC.

Results

There were 81 patients at VUMC who met the criteria for analysis (Table 1). The median age was 70, and 60%

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Table 1
Patient characteristics.

	All Patients (N = 81)
Age (median, IQR[a])	70 (59–76)
Sex (%)	
Male	49 (60)
Female	32 (40)
Cancer Type (%)	
Lung cancer	22 (27)
Melanoma	19 (23)
Kidney cancer	11 (14)
GI/Hepatic cancer	9 (11)
Head and Neck	7 (9)
Other	13 (16)
Immune checkpoint inhibitor (%)	
Pembrolizumab	45 (56)
Nivolumab	22 (27)
Durvalumab	6 (7)
Cemiplimab	5 (6)
Atezolizumab	3 (4)
Prior irAE (%)	9 (11)
Hypothyroidism	3 (3.7)
Hepatitis	2 (2.5)
Adrenal Insufficiency	1 (1.2)
Diabetes	1 (1.2)
Arthritis	1 (1.2)
Immune-mediated thrombocytopenia	1 (1.2)
Months on ICI[b] (median months, IQR[a])	6.6 (2.1–11.2)
Days between most recent ICI prior to second dose of vaccine (median days, IQR[a])	13 (8–20)
Covid-19 vaccine	
BNT 162b2 (Pfizer-BioNTech)	67 (83)
mRNA-1273 (Moderna)	14 (17)

[a] IQR: interquartile range.
[b] ICI: immune checkpoint inhibitor.

were male. The most common cancer subtype was lung (27%), followed by melanoma (23%), kidney cancer (14%), and gastrointestinal/hepatic cancer (11%). Most patients received pembrolizumab (56%) or nivolumab (27%). The median duration of ICI treatment prior to vaccination was 6.6 months [interquartile range (IQR): 2.1–11.2]. The median duration between the most recent ICI infusion and the second dose of the COVID-19 vaccine was 13 days (IQR: 8–20). 9 patients (11%) had irAEs prior to COVID-19 vaccination (all $\leq$ grade 2). Patients received either the Pfizer-BioNTech (83%) or Moderna (17%) COVID-19 vaccine. 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%) patients had exacerbation of previous irAEs or diagnosis of new irAEs. One patient died during the 30-day follow-up due to cancer progression.

As of the cut-off date of 14th May 2021, there were 152,748 adverse events following the administration of COVID-19 mRNA vaccines reported to the VAERS. There were 24 events reported in patients concurrently receiving ICIs, and six of them had clinical presentations suspicious for irAEs (Table 2), including two with possible flares of pre-existing irAEs and four *de novo* irAEs.

Discussion

We observed no signal of increased risk of development or exacerbation of irAEs after mRNA COVID-19 vaccination (either the Pfizer-BioNTech or Moderna vaccine) among cancer patients who were on active treatment with ICIs. These results support prior work, [6], which suggested no new or exacerbation of irAEs after administration of the Pfizer-BioNTech vaccine among 134 ICI-treated cancer patients. Further, after investigating the 152,748 adverse events in the VAERS, there were only six adverse events, which were suspicious for irAEs following COVID-19 vaccine administration. Given the large number of

Table 2
Cases suspicious for irAEs following COVID-19 mRNA vaccine administration.

Age/ Sex[a]	Cancer	ICI[b]	Vaccine manufacturer	Symptoms onset after vaccination	Symptoms or diagnosis	Comments
79/F	Lung cancer	Pembrolizumab	Pfizer-BioNTech	7 days	Respiratory distress	History of pembrolizumab associated pneumonitis
37/M	Thymus cancer	Pembrolizumab	Pfizer-BioNTech	1 day	Acute hemolytic anemia	Labs consistent with haemolytic anaemia
48/M	Kidney cancer	Ipilimumab/nivolumab	Moderna	Same day	Shock requiring pressor support	Home medication includes hydrocortisone 10 mg/5 mg; history of adrenal insufficiency
70/M	Prostate cancer	Pembrolizumab	Pfizer-BioNTech	1 day	Myositis	Labs/Imaging work-up consistent with inflammatory myositis; last pembrolizumab was 2 months ago
77/F	Lung cancer	Pembrolizumab	Pfizer-BioNTech	4 days	Cardiogenic shock	Coronary angiography showed no significant narrowing or blockage; labs showed elevated troponins
68/M	Sarcoma	Pembrolizumab	Moderna	5 days	Pancreatitis/rash	No prior history of pancreatitis

[a] M: male; F: female.
[b] ICI: immune checkpoint inhibitor.

patients receiving ICIs, this is likely consistent with the background rate of irAEs. However, the VAERS is limited by its passive reporting system and cannot be used to establish causal effects of a given vaccine and cannot establish frequency data. Our study helps supplement the limited data available regarding the safety and risk of irAE of vaccination among patients with cancer receiving ICIs [7,8]. Considering the high mortality rate from COVID-19 among cancer patients [1], the benefit of COVID-19 vaccination exceeds the hypothetical increased risk of irAEs for patients receiving ICIs, which appears minimal or non-existent in this and other series. Limitations of this study include the retrospective nature, duration of follow up, and limited sample size. In summary, the current findings support major society guidelines to offer COVID-19 vaccines to cancer patients receiving ICIs [2–4].

Conflict of interest statement

Yu-Wei Chen: None.

Matthew Tucker: None.

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