

COVID-19 vaccination in patients with cancer receiving immune checkpoint inhibitors: a systematic review and meta-analysis

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ABSTRACT

Background Immune checkpoint inhibitors (ICI) can cause off-target inflammatory and immune-related adverse events (irAE). Conceivably, COVID-19 vaccination could trigger an inflammatory and immune response that could induce or aggravate irAE.

Methods The objective of this systematic review is to appraise the efficacy and safety of COVID-19 vaccination in patients with cancer treated with ICI. The literature search was performed in PubMed and Embase in English from December 2019 to February 2022. The review included clinical trials, observational cohort studies, case series, and case reports reporting on the clinical efficacy and safety of COVID-19 vaccines on patients with cancer treated with ICI. Outcomes of interest included seroconversion, SARS-CoV-2 infection rate, severe COVID-19, COVID-19 mortality rate. Incidence of ICI irAEs was also ascertained as well as vaccine adverse events. A meta-analysis was conducted to estimate the pooled effect sizes of the outcomes when possible, using random effects models.

Results Overall, 19 studies were included for the analysis (n=10 865 with 2477 receiving ICI). We analyzed 15 cohort studies, 1 cross-sectional study, and 3 case reports. There were no statistically significant differences in seroconversion rates after the second dose of the vaccine when comparing patients with cancer receiving ICI with patients without cancer (risk ratio, RR 0.97, 95% CI 0.92 to 1.03) or with patients with cancer without active treatment (RR 1.00, 95% CI 0.96 to 1.04). There was a higher probability of seroconversion in patients with cancer treated with ICI compared with patients with cancer treated with chemotherapy (RR 1.09, 95% CI 1.00 to 1.18). In a single study in patients receiving ICI, no differences were observed in risk of irAE between those receiving inactivated vaccine and those unvaccinated (pneumonitis RR 0.88, 95% CI 0.33 to 2.3; rash RR 1.03, 95% CI 0.66 to 1.62; arthralgia RR 0.94, 95% CI 0.51 to 1.75). There were no studies for other types of vaccines comparing vaccinated vs not vaccinated in patients treated with ICI. The most common vaccine-related adverse events were local pain or fatigue. Overall, the quality of evidence was rated as very low.

Conclusion COVID-19 vaccination appears to be effective and safe in patients with cancer receiving ICI.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ It has been suggested that COVID-19 vaccines might lead to immune-related adverse event in patients receiving immune checkpoint inhibitor (ICI). Clinical trials that evaluated the efficacy of these vaccines did not include patients with cancer receiving treatment. Several small studies have been published with heterogeneous methods and results.

WHAT THIS STUDY ADDS

⇒ COVID-19 vaccination appears to be safe and effective in patients with cancer receiving ICI, although the quality of the evidence is low.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ COVID-19 vaccination can be recommended for patients with cancer receiving ICI. However, additional well-controlled studies are needed to robustly assess the impact of vaccination in this population with respect to clinical outcomes such as incidence and severity of COVID-19.

BACKGROUND

As we face the third year of the COVID-19 pandemic, vaccination against COVID-19 has exponentially increased, including patient populations with chronic disease. Up to March 2022, 149 COVID-19 vaccines were in clinical development.¹ Available vaccines are highly effective for the prevention of severe COVID-19 and mortality. A recent meta-analysis of 35 randomized control trials showed that the efficacy of vaccines to prevent COVID-19 infection was 95% (95% CI 92% to 97%) for mRNA vaccines, 68% (95% CI 61% to 74%) for viral vector vaccines, and 61% (95% CI 52% to 68%) for inactivated vaccines.² None of the trials included pregnant women or immunocompromised participants such as patients with cancer.³

Patients with cancer are at high risk of COVID-19 severe complications and death.

Those who are receiving oncological treatment when they acquire COVID-19 have higher risks of death, hospitalization, and intensive care unit (ICU) admission compared with patients with cancer without recent cancer treatment, or patients without cancer.⁴ COVID-19 vaccination is highly recommended for patients with cancer, despite a concern about potentially lower efficacy in immunosuppressed patients.⁵ Moreover, it has been suggested that COVID-19 vaccination may be a risk factor for immune-related adverse event (irAE) in patients with cancer receiving immune checkpoint inhibitor (ICI).^{6–8} Conceivably, both the COVID-19 vaccination and the ICI can independently stimulate the immune system potentiating adverse events.⁶ Prior literature on the use of influenza vaccination in patients with cancer receiving ICI, suggests that it is safe.⁹

However, to the best of our knowledge, there are no prior systematic reviews specifically evaluating COVID-19 vaccination in patients with cancer receiving ICI. The aim of this systematic review and meta-analysis is to determine the efficacy and safety of COVID-19 vaccination in this population.

METHODS

This study was registered at PROSPERO (registration number: CRD42022307545; <http://www.crd.york.ac.uk/PROSPERO>). This study was conducted in accordance with the Preferred Reporting Items of Systematic Reviews and Meta-analyses statement.

Eligibility criteria

We included clinical trials, cohort studies (prospective and retrospective), and cross-sectional studies. We also included case series and case reports to identify unusual adverse events potentially associated with vaccination.

We included studies of adults (≥ 18 years old) with any type of cancer receiving ICI who underwent COVID-19 vaccination. Immune checkpoint inhibitors included: (1) programmed cell death protein 1 (PD-1) inhibitors (pembrolizumab, nivolumab, cemiplimab); programmed death-ligand 1 (PD-L1) inhibitors (atezolizumab, avelumab, durvalumab); and the cytotoxic T lymphocyte-associated protein 4 inhibitor ipilimumab. We considered any comparison group (eg, chemotherapy, no active treatment, healthy individuals). We excluded studies if insufficient information for analysis was provided, studies where the type of immunotherapy received was not specified, and studies on pediatric populations. We included the following 10 COVID-19 vaccines granted emergency use by the WHO: (1) protein subunit vaccines (Novavax (NVX-CoV2373) and COVOVAX of the Serum Institute of India), (2) mRNA vaccines (Moderna (mRNA-1273) and Pfizer/BioNTech (BNT162b2)), (3) non replicating viral vector vaccines (Janssen (Ad26.COV2.S); Oxford/AstraZeneca (ChAdOx1 nCoV-19); and Covishield of the Serum Institute of India), (4) inactivated vaccines (Bharat Biotech – Covaxin (BBV152)); Sinopharm

(BBIBP-CorV); and Sinovac (CoronaVac)). The outcomes of interest were: seroconversion, COVID-19 infection, severe COVID-19, COVID-19 mortality, vaccine adverse events (local and systemic), irAE.

Information sources

An expert librarian searched two electronic databases Ovid Medline and Ovid Embase from December 1, 2019 to February 05, 2022. We also manually reviewed the references in other reviews of COVID-19 vaccination in patients with cancer.

Search strategy

The search included terms related to coronavirus vaccination, cancer, and ICI (online supplemental tables S1 and S2).

We used EndNote V.X9 (Clarivate) to manage references.

Selection process, data collection process and data items

Two reviewers (JIR and MAL-O) independently screened the citations and reviewed the studies of interest for inclusion. Disagreements were resolved by discussion. Data was extracted by one reviewer (JIR) and cross-checked by a second reviewer (MAL-O). The following information was extracted for each included study: (1) general study information (ie, year of publication, country, study design), (2) population characteristics (ie, age, gender, number of patients), (3) intervention characteristics (ie, number of patients under ICI treatment, number of patients in comparison group, interval between COVID-19 vaccine and outcome assessment, types of ICI, types of comparison (chemotherapy, no treatment, healthy individuals) and (4) outcomes: severe disease (according to each publication authors' definition), ICU admission, mechanical ventilation, mortality, seroconversion, rate of irAE and type of irAE.

Study risk of bias assessment

The risk of bias was assessed by two reviewers (JIR and MAL-O) and discrepancies were resolved by discussion. We used the Newcastle-Ottawa Scale (NOS) to assess the methodological quality of observational studies. This scale consists of three components: patient selection, study comparability, and outcome assessment, with scores ranging from 0 to 9 (best).

Synthesis methods

We performed the statistical analysis using Review Manager V.5.3 (RevMan).

Effect measures

We presented the measure of association as risk ratios (RRs) and their corresponding 95% CI. If the data were not suitable for pooling, we synthesized the results narratively.

Processes used to decide which studies were eligible for synthesis

In order to decide which studies were eligible for each synthesis we specified and tabulated the study

characteristics (population, intervention, the comparisons groups, and the outcomes).

Methods required to prepare the data for synthesis

We calculated the RRs when study provided raw data on frequency of events and sample sizes. We used the Mantel-Haenszel method for meta-analysis of dichotomous raw data. Adjusted estimates were used where possible for primary analyses, to decrease potential confounder bias. Data were pooled using random effects models.

Heterogeneity

We assessed heterogeneity using I^2 statistics. We considered that heterogeneity was present when the I^2 was higher than 40%.

Methods to explore heterogeneity

We grouped studies by type of vaccine, and type of design (prospective vs retrospective) to determine their potential effect on the results.

Additional analyses

In order to evaluate the occurrence of unusual adverse events of ICIs in patients with COVID-19 immunization, we summarized case reports and case series that identified irAE that may not be detected in longitudinal observational studies.

Reporting bias assessment

We planned a priori to assess and quantify publication bias using funnel plots and Egger's test if more than 10 studies reported on the primary outcome. However, data were insufficient to perform this analysis.

Certainty assessment

We evaluated the quality of the evidence for each outcome using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework, which considers risk of bias, indirectness, inconsistency, imprecision, and publication bias.¹⁰ We created summary of findings tables (SoF), which synthesize the most important results of a review in a structured format that is transparent providing information about the quality of evidence and the magnitude of the effects of the outcomes of interest, including the following information for each of the important outcomes (desirable and undesirable)¹¹: (1) the relative effect of the intervention, (2) the baseline risk (control group), (3) the absolute risk of the intervention group, (3) the number of studies and number of participants, and (4) the confidence in the effect estimates or certainty of the evidence.¹² The RR with its 95% CI was obtained from the meta-analyses performed for each outcome and comparison. The absolute risks for each comparison groups were obtained from the representative studies of the review or the median comparator group risk across studies. The intervention absolute risk was obtained from the following calculation:

$$\text{absolute risk with the intervention} = \text{absolute risk with the comparator} \times \text{RR} \times 1000$$

The certainty of the evidence was assessed using the specific grading system of the GRADE working group that considers the following domains: (1) risk of bias (ie, the confidence on the estimate of effect decreases because there are limitations in the study design), (2) inconsistency (ie, when the estimates of effect vary widely from one study to the other and there are no explanations for this heterogeneity), (3) indirectness (ie, the estimate of effect comes from studies with different population, and/or intervention, and/or comparison, and/or outcome from our main review question), (4) imprecision (ie, the studies include few number of participants and/or events or the 95% CI includes both benefits and harms for the patients), and (5) publication bias (ie, when investigators do not report studies because of lack of effect or selecting and non-reporting outcomes). The certainty or quality of the evidence was rated as high (indicating that further research is very unlikely to change our confidence in the estimate of effect), moderate (indicating that further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate), low (indicating that further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate) or very low (indicating that any estimate of effect is very uncertain).

RESULTS

Search results

The strategy identified 191 citations (figure 1). After removing duplicated studies, we screened 147 citations. We included 37 studies for full text assessment. Finally, 19 studies were eligible to include for analysis.^{13–31} A total of 10 865 participants were included in the analysis and 2477 received ICI.

Description of included studies

Study characteristics are described in table 1. Considering the type of studies included, 3 were case reports, 15 cohort studies, and 1 cross-sectional study. The range of ages included were 16–93 and the average of male participants was 52%. The types of vaccines included were: BNT162b2 (Pfizer) in 16 (84%) studies,^{13–16 18 20 21 23–25 27–31} mRNA-1273 (Moderna) in 8 (42%) studies,^{17–19 25–27 29 30} Ad26.COVS2 (Janssen) in 3 (16%) studies,^{25 27 30} Sinovac in 1 (5%) studies,²² Sinopharm in 1 (5%) study,²² ChAdOx1 nCoV-19 (AstraZeneca) in 1 (5%) study.²⁷ With regard to the outcomes, 12 studies reported immunogenicity as humoral response 14–30 days after the second dose of the vaccine,^{13 16 18–23 25 26 29 30} 10 studies reported irAE,^{14 15 17 20 22 24 26 27 29 31} 9 reported vaccine-related adverse events (VrAE),^{16 20 21 25 26 28 29 31} and 3 reported incidence of COVID-19.^{20 21 29} The characteristics of the participants included in the studies are in table 2. The types of cancer included and the funding information for each study are shown in online supplemental table S3.

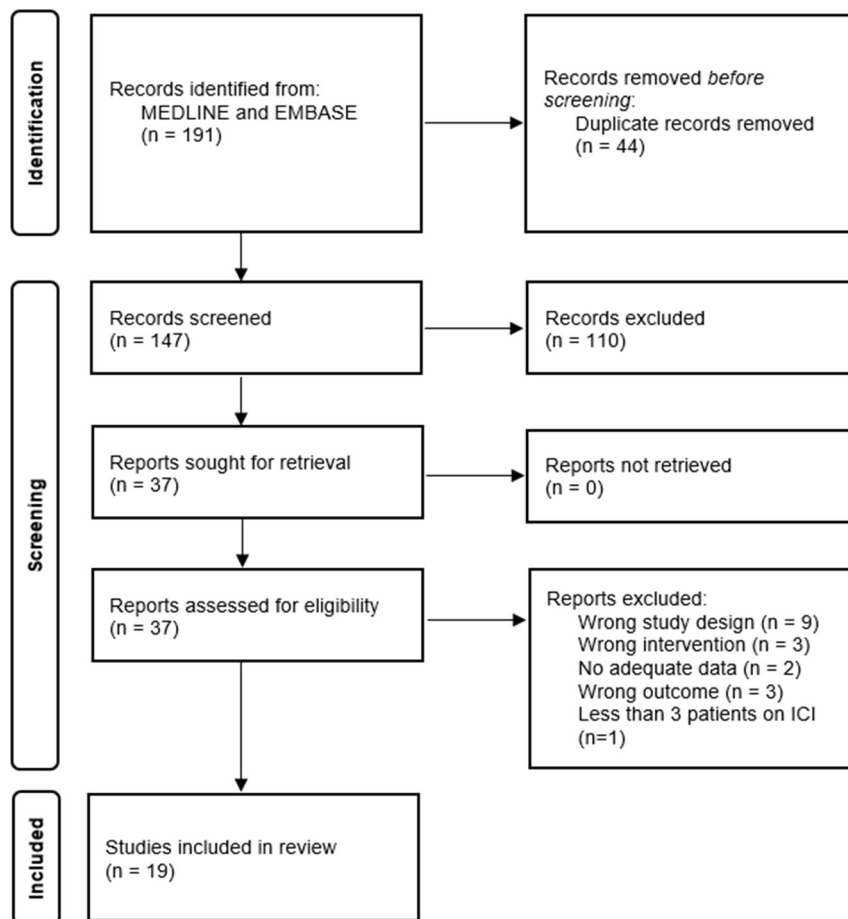


Figure 1 Flow diagram of study selection.

Observational studies

The reported rates of seroconversion and adverse events of individual studies are shown in online supplemental table S4.

Seroconversion

Patients with cancer treated with ICI compared with controls without cancer (figure 2) (7 studies^{13 18 21–23 26 30} including 473 patients on ICI and 747 controls). No statistically significant differences were observed in the pooled estimate (RR 0.97, 95% CI 0.92 to 1.03). However, when analyzing the subgroups by type of vaccines, the risk of seroconversion with the inactivated vaccines Sinopharm or Sinovac was lower in patients with cancer treated with ICI compared with individuals without cancer (RR 0.85, 95% CI 0.74 to 0.97).

Patients with cancer treated with ICI compared with patients with cancer treated with chemotherapy (figure 3) (9 studies^{13 16 18 19 21 23 25 26 30} including 439 patients on ICI and 778 patients on chemotherapy). The RR for this comparison was 1.09 (95% CI 1.00 to 1.18) favoring patients treated with ICI.

Patients with cancer treated with ICI compared with patients with cancer without active treatment (figure 4). Three studies^{16 19 25} reported seroconversion for this comparison including 104 patients on ICI and 228 patients with cancer without active treatment. No

statistically significant differences were observed in the pooled estimate (RR 1.00, 95% CI 0.96 to 1.04).

COVID-19 infection

Three studies^{20 21 29} evaluated the incidence of COVID-19 infection including 155 patients with cancer treated with ICI. There were no COVID-19 infection cases documented during the period of the studies. As no COVID-19 infections were reported, severity and mortality could not be evaluated.

Vaccine-related adverse events

Ten studies^{16 20–22 25–29 31} reported the frequency of VrAE in patients with cancer treated with ICI and who received the COVID-19 vaccine. The results for individual studies are shown in online supplemental table S3. Overall, most of the VrAE were mild or moderate, with local pain and fatigue as the most common VrAE. The range of rate of fatigue was from 24% to 59%, the range of local pain was from 6% to 63%. In one study²² that used the inactivated vaccines Sinovac and Sinopharm there was a statistically significant difference in rash comparing patients who received ICI vs those who did not receive ICI (OR 3.5, 95% CI 1.67 to 7.35 $p < 0.001$).

Patients with cancer treated with ICI compared with controls without cancer. One study²⁶ (VOICE trial)

Table 1 Characteristics of included studies

Study ID	Country	Health centers n	Period	Vaccine	Total n	Outcomes	Seroconversion cut-off
Retrospective cohort studies							
Chen <i>et al</i> 2021 ¹⁷	USA	1	NR	BNT162b2 (Pfizer) and mRNA-1273 (Moderna)	81	irAE, VrAE	–
Ligumsky <i>et al</i> 2021 ²¹	Israel	1	March–April 2021	BNT162b2 (Pfizer)	490	Immunogenicity (humoral response), VrAE	>50 AU/mL
Ma <i>et al</i> 2021 ²²	China	4	NR	CoronoVac (Sinovac) and Beijing Bio-Institute of Biological Products (Sinopharm)	660	Immunogenicity (humoral response), irAE	–
Strobel <i>et al</i> 2021 ²⁷	Germany	1	March–July 2021	BNT162b2 (Pfizer), mRNA-1273 (Moderna), ChAdOx1 nCoV-19 (AstraZeneca), and Ad26.COV2S (Janssen)	130	irAE	–
Svoboda <i>et al</i> 2021 ²⁹	USA	NR	July 2020–June 2021	BNT162b2 (Pfizer) and mRNA-1273 (Moderna)	23	Immunogenicity (humoral response), VrAE, irAE	Receptor binding domain >0.700 AU
Prospective cohort studies							
Buttiron-Webber <i>et al</i> 2021 ¹⁶	Italy	NR	NR	BNT162b2 (Pfizer)	320 (291 analyzed)	Immunogenicity (humoral response), VrAE	>25 AU/mL
Di Giacomo <i>et al</i> 2021 ¹⁸	Italy	NR	NR	BNT162b2 (Pfizer) for healthy hospital personnel and mRNA-1273 (Moderna) for patients with cancer	173	Immunogenicity (humoral response)	>50 AU/mL
Figueiredo <i>et al</i> 2021 ¹⁹	USA	1	December 2020–August 2021	BNT162b2 (Pfizer) and mRNA-1273 (Moderna)	1697	Immunogenicity (humoral response)	>50 AU/mL
Lasagna <i>et al</i> 2021 ²⁰	Italy	Multi-center	March–April 2021	BNT162b2 (Pfizer)	88	Immunogenicity, incidence of COVID-19, VrAE, irAE	>15 AU/mL
Massarweh <i>et al</i> 2021 ²³	Israel	1	February–March 2021	BNT162b2 (Pfizer)	180	Immunogenicity (humoral response)	>50 AU/mL
Naranbhai <i>et al</i> 2021 ²⁵	USA	1	April–July 2021	BNT162b2 (Pfizer), Ad26.COV2S (Janssen), mRNA1273 (Moderna)	762*	Immunogenicity, VrAE	Index >0.8
Oosting <i>et al</i> 2021 (VOICE trial) ²⁶	Netherlands	Multi-center: 3	February–March 2021	mRNA-1273 (Moderna)	750	Immunogenicity (humoral response), VrAE, irAE	>10 AU/mL
Subbiah <i>et al</i> 2021 ³²	USA	1	NR	BNT162b2 (Pfizer)	4714	VrAE (Patient reported outcomes)	–
Thakkar <i>et al</i> 2021 ³⁰	USA	NR	NR	BNT162b2 (Pfizer), mRNA-1273 (Moderna), Ad26.COV2S (Janssen)	242†	Immunogenicity (humoral response)	>50 AU/mL
Waissengrin <i>et al</i> 2021 ³¹	Israel	1	January–February 2021	BNT162b2 (Pfizer)	268	VrAE, IrAE	–
Cross-sectional studies							
Agbarya <i>et al</i> 2021 ¹³	Israel	Multi-center: 2	February–April 2021	BNT162b2 (Pfizer)	355	Immunogenicity (humoral response)	>150 AU/mL
Case reports							
Au <i>et al</i> 2021 ¹⁴	UK	NR	December 2020	BNT162b2 (Pfizer)	–	irAE (cytokine release syndrome)	–

Continued

Table 1 Continued

Study ID	Country	Health centers n	Period	Vaccine	Total n	Outcomes	Seroconversion cut-off
Blaise <i>et al</i> 2021 ¹⁵	France	NR	January 2021	BNT162b2 (Pfizer)	–	irAE (necrotizing myopathy – Grade 4)	–
Mieczkowska <i>et al</i> 2021 ²⁴	USA	NR	NR	BNT162b2 (Pfizer)	–	irAE (Psoriasis exacerbation)	–

*Excluding the healthy controls reported in the literature previously.

†200 analyzed for efficacy.

ICI, immune checkpoint inhibitor; irAE, immune-related adverse events; NA, not applicable; NR, not reported; VrAEs, vaccine-related adverse events.

including 137 patients on ICI and 240 controls reported VrAE. No statistically significant differences were observed for the following adverse events: fatigue (RR 1.09, 95% CI 0.91 to 1.31 $p=0.36$), pain (RR 1.60, 95% CI 0.63 to 4.06 $p=0.32$), VrAE grade 3 or worse (RR 12.22, 95% CI 0.64 to 234.9 $p=0.1$).

Patients with cancer treated with ICI compared with patients with cancer treated with chemotherapy. One study²⁶ including 137 patients on ICI and 244 on chemotherapy reported VrAE. No statistically significant differences were observed for the following adverse events: fatigue (RR 1.21, 95% CI 0.99 to 1.47 $p=0.06$), pain (RR 1.25, 95% CI 0.52 to 3.03 $p=0.62$), VrAE grade 3 or worse (RR 0.89, 95% CI 0.23 to 3.50 $p=0.87$).

Immune-related adverse events

Six studies^{17 20 22 26 27 31} reported the frequency of irAE in patients with cancer treated with ICI and who received the COVID-19 vaccine. The results of individual studies are shown in online supplemental table S3. The range of rate of irAE was from 0% to 23.6%. No unusual adverse events were reported.

There was only one study²² that reported the risk of irAE comparing patients treated with ICI who received the vaccine versus those who did not receive it. This study evaluated the inactivated vaccines Sinopharm and Sinovac including 127 patients on the vaccine group and 127 patients on the non-vaccine group performing a propensity score matched analysis. No statistically significant differences were observed for pneumonitis (RR 0.88, 95% CI 0.33 to 2.31 $p=0.79$), rash (RR 1.03, 95% CI 0.66 to 1.62 $p=0.88$), diarrhea (RR 0.82, 95% CI 0.35 to 1.91 $p=0.64$), arthralgia (RR 0.94, 95% CI 0.51 to 1.75 $p=0.86$), liver function test abnormalities (RR 1.07, 95% CI 0.55 to 2.06 $p=0.85$).

Risk of bias

We used the NOS to assess the risk of bias of the 16 observational studies, (online supplemental table S5). The scores ranged from 3 to 8 (maximum score 9). Nine (56%) of the studies^{13 16–18 20 27 29 31 32} had high risk of confounding bias as they did not adjust for potential confounders.

Summary of findings

The summary of findings tables with the certainty of evidence of the different comparisons are shown in

online supplemental tables S6–8. The absolute benefit of seroconversion in patients with cancer treated with ICI was: (1) 922 per 1000 (between 874 and 970 per 1000) compared with 950 per 1000 in individuals without cancer, (2) 974 per 1000 (between 935 and 1000 per 1000) compared with 974 per 1000 in patients with cancer without active treatment, and (3) 958 per 1000 (between 879 and 1000 per 1000) compared with 879 per 1000 in patients with cancer treated with chemotherapy. The absolute risk of grade 3 or more VrAE in patients with cancer treated with ICI was 8 per 1000 (between 2 and 29 per 1000) compared with 8 per 1000 in patients with cancer treated with chemotherapy.

For all the comparisons and outcomes, the certainty of the evidence was rated as very low because the risk of bias of the primary studies and downgraded for imprecision. We also downgraded the quality of evidence for indirectness because seroconversion was considered a surrogate outcome.

Case reports

We found three case reports^{14 15 24} that reported unusual adverse events in patients with cancer treated with ICI who received the COVID-19 vaccine. In the three cases the patients received the BNT162b2 vaccine. One of the patients presented cytokine release syndrome, another patient necrotizing myopathy grade four and the third case exacerbation of psoriasis.

The studies excluded and the reasons for exclusions are presented in online supplemental table S9.

DISCUSSION

To our knowledge, this is the first systematic review evaluating the efficacy and safety of COVID-19 vaccines in patients with cancer receiving ICI. Previous systematic reviews and meta-analyses^{33 34} have reported on the outcomes of COVID-19 vaccines in patients with cancer at large, but not specifically in those receiving ICI. Becerrill-Gaitan *et al* showed that patients with cancer were less likely to seroconvert after complete vaccination compared with non-cancer controls (RR 0.69, 95% CI 0.65 to 0.84).³³ Nevertheless, they did not analyze the effect of the different cancer treatment on the efficacy of the vaccine. A narrative review included information in

Table 2 Characteristics of patients included in the studies

Study ID	Age	Types of ICI	Non-ICI interventions	Interval between second vaccine and evaluation of outcome	% of patients with prior COVID-19 infection
Agbarya <i>et al</i> 2021 ¹³	65.3 (mean)	Pembrolizumab, nivolumab, ipilimumab, durvalumab, avelumab, atezolizumab, cemiplimab (n=43)	Chemotherapy (n=73), biological drugs (24), healthy subjects (n=215)*	14 days	NR
Au <i>et al</i> 2021 ¹⁴	>18†	Anti-PD-1 monotherapy (n=1)	NA	5 days	NR
Blaise <i>et al</i> 2021 ¹⁵	>18†	Pembrolizumab, nivolumab (1 mg/kg) plus ipilimumab (3 mg/kg) (n=1)	NA	10 days (after first vaccine)	NR
Buttiron Webber <i>et al</i> 2021 ¹⁶	68 (median)	Unspecified ICI (n=21)	Chemotherapy (n=115), hormone therapy (n=70), targeted therapy (n=23), patients with cancer with no active treatment (n=62)	21 days	11.3
Chen <i>et al</i> 2021 ¹⁷	70 (median)	Pembrolizumab (n=45), nivolumab (n=22), durvalumab (n=6), cemiplimab (n=5), atezolizumab (n=3)	NA	30 days (at least)	NR
Di Giacomo <i>et al</i> 2021 ¹⁸	NR	Unspecified ICI (n=70)	Chemotherapy (n=28), Targeted therapy (n=23), healthy subjects (n=42),	18 days (median)	0
Figueiredo <i>et al</i> 2021 ¹⁹	65 (median)	Unspecified vaccinated ICI (n=74)	healthcare workers (n=1245) Unvaccinated patients with cancer (n=54), vaccinated patients with cancer (n=291)	42 days (median)	Vaccinated: 6.2 Unvaccinated: 22.2
Lasagna <i>et al</i> 2021 ²⁰	68 (median)	PD-1/PD-L1 (n=88)	NA	21 days	14.8
Ligumsky <i>et al</i> 2021 ²¹	66 (median)	Unspecified ICI (n=55)	Chemotherapy (n=101), Combination (n=104)‡, targeted therapy (n=38), other treatments (n=28)‡, healthy subjects (n=164)*	78 days	NR
Ma <i>et al</i> 2021 ²²	50.3 (mean)	Nivolumab (n=51), pembrolizumab (n=49), sintilimab (n=76), toipalimab (n=44), tislelizumab (n=31), camrelizumab (n=39). Patients were divided in PD-1 vaccinated (n=138) and PD1 unvaccinated (n=152)	Patients with cancer without PD-1 (n=164), non-cancer patients (n=206)	1–3 months	NR
Massarweh <i>et al</i> 2021 ²³	66 (median)	Unspecified ICI (n=22)	Chemotherapy (n=30), chemotherapy plus biological therapy (n=20), biological therapy (n=11), healthy subjects (n=78)	38 days	NR
Mieczkowska <i>et al</i> 2021 ²⁴	> 18†	Nivolumab (n=1)	NA	7 days (after first dose)	NR
Naranbhai <i>et al</i> 2021 ²⁵	66 (median)	Unspecified ICI (n=70)	No systemic treatment (n=205), healthy subjects (n=418), chemotherapy (n=101), targeted therapy (n=149), combination (n=124)	7 days	
Oosting <i>et al</i> 2021 (VOICE trial) ²⁶	66 (median)	Nivolumab (n=66), pembrolizumab (n=36), cemiplimab (n=7), atezolizumab (n=5), avelumab (n=5), duvalumab (n=2)	Chemotherapy (n=229), chemotherapy plus immunotherapy (n=143), healthy patients (n=247)	28 days	NR

Continued

Table 2 Continued

Study ID	Age	Types of ICI	Non-ICI interventions	Interval between second vaccine and evaluation of outcome	% of patients with prior COVID-19 infection
Strobel <i>et al</i> 2021 ²⁷	64 (median)	Pembrolizumab (n=45), nivolumab (n=14), cemiplimab (n=4), avelumab (n=6), combination ICI (n=20)	Non-ICI systemic therapies (n=108), unvaccinated patients with cancer (n=19)	84 days	NR
Subbiah <i>et al</i> 2021 ³²	54 (median)	Unspecified ICI (n=857)	NA	NR	NR
Svoboda <i>et al</i> 2021 ²⁹	42 (median)	PD-1 (n=23)	NA	–	26
Thakkar <i>et al</i> 2021 ³⁰	67 (median)	Unspecified ICI (n=31)	Non-cancer patients (n=26), non-ICI treatments (n=169)	7 days	11
Waissengrin <i>et al</i> 2021 ³¹	72 (median)	Unspecified ICI (n=97)	Healthy subjects (n=134)	19 days	NR

*Patients' relatives, healthcare workers, and volunteers.
†Exact patient age not provided as required by the journal.
‡Includes patients receiving other treatments plus ICI.
ICI, immune checkpoint inhibitor; NA, not applicable; NR, not reported; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1.

patients treated with ICI suggesting that efficacy and safety were similar to that observed in the general population.⁷

The results of our systematic review suggest that COVID-19 vaccines are effective in patients with cancer treated with ICI, as determined by seroconversion rates.

We found no significant differences in the rate of seroconversion after the second dose of the vaccine when comparing patients with cancer receiving ICI versus healthy participants. However, the frequency of seroconversion with the inactivated vaccines Sinopharm or

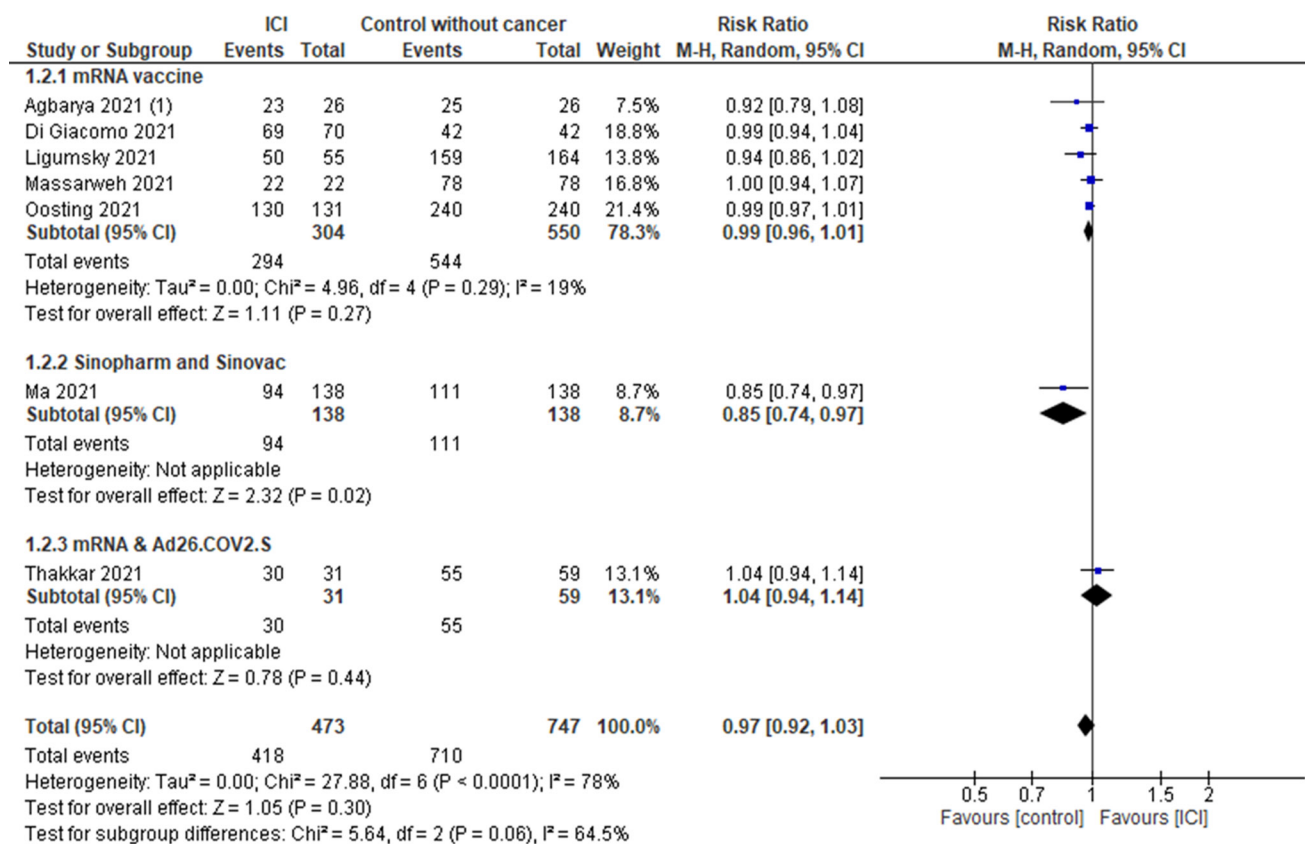


Figure 2 Risk of seroconversion after COVID-19 vaccination in patients with cancer treated with ICI versus control without cancer. ICI, immune checkpoint inhibitor.

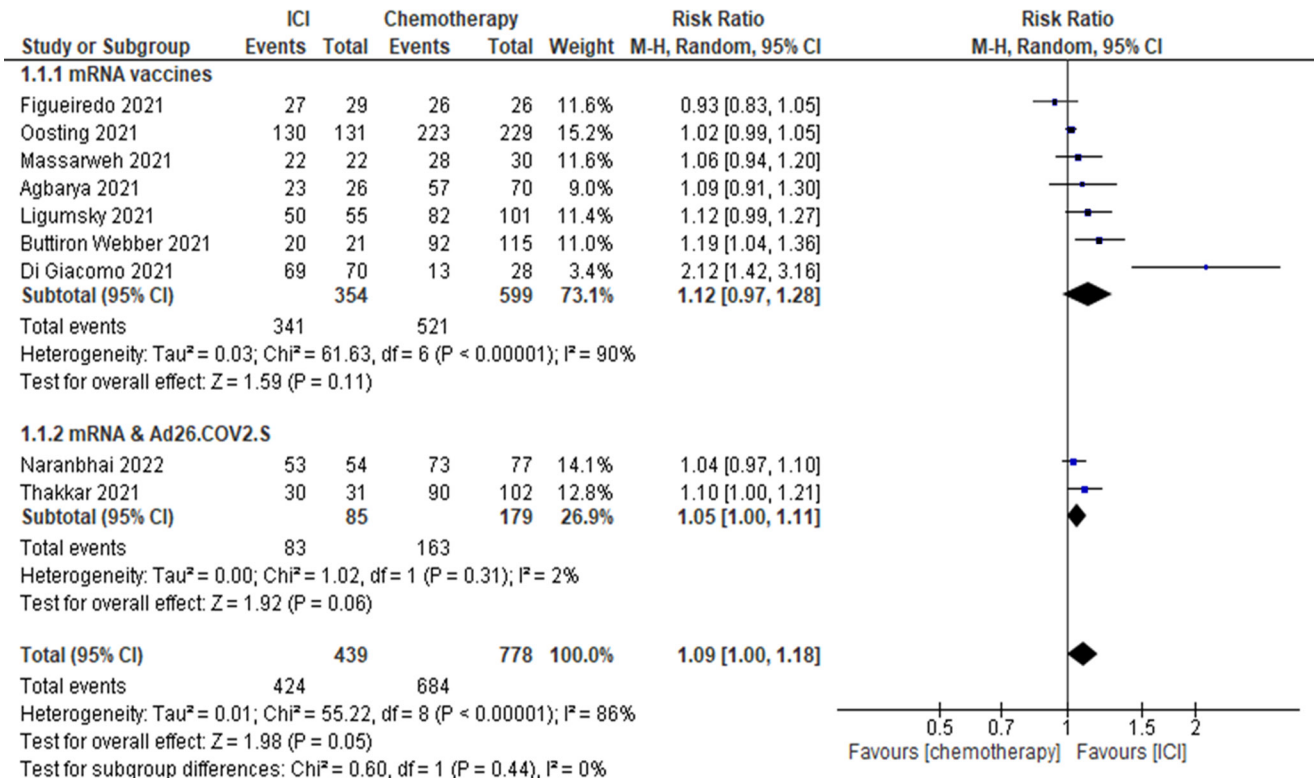


Figure 3 Risk of seroconversion after COVID-19 vaccination in patients with cancer treated with ICI versus patients with cancer treated with chemotherapy. ICI, immune checkpoint inhibitor.

Sinovac was significantly lower in patients with cancer treated with ICI compared with individuals without cancer. Patients with cancer treated with ICI showed a higher probability of seroconversion than patients with cancer treated with chemotherapy. Rates of COVID-19 infection were evaluated in three small studies, and none of the 155 patients receiving ICI developed COVID-19. Therefore, the impact of vaccination on clinically important outcomes such as hospital admissions, use of mechanical ventilation or death, could not be assessed.

As treatment with ICI enhances immune responses, there have been theoretical concerns that concomitant treatment with ICI and receipt of the COVID-19 vaccination, could result in increased risk of irAE.⁶ Only one study²² reported irAE comparing patients on ICI who received the inactivated vaccines Sinopharm and Sinovac vaccines with those who did not receive vaccination, and found no statistically significant differences between the two groups. Other studies reported rates of irAE with mRNA vaccines, ranging 0%–24%, but they did not have

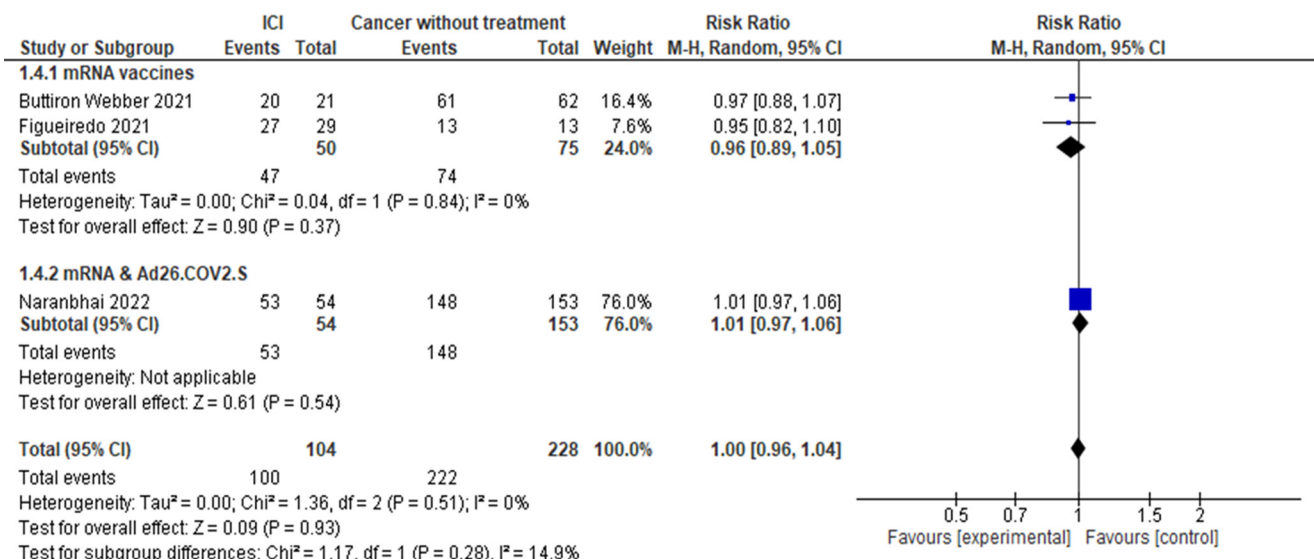


Figure 4 Risk of seroconversion after COVID-19 vaccination in patients with cancer treated with ICI versus patients with cancer without treatment. ICI, immune checkpoint inhibitor.

suitable control groups of unvaccinated patients receiving ICI. These rates, however, seem similar to the observed rates of irAE in studies of patients receiving ICI (not related to vaccination).^{35–37} Moreover, most of the irAE were low grade. No unusual adverse events were reported in these studies.

With regard to the adverse events related to the vaccination, most of them were local pain and fatigue with a range of 6%–63% and 24%–59%, respectively. Most of the VrAE reported were mild or moderate. In the study of patients who received the inactivated vaccines Sinovac and Sinopharm²² there was a higher risk of developing rash in patients treated with ICI compared with those not treated with ICI. The VOICE trial²⁶ that evaluated the safety and efficacy of the mRNA-1273 vaccine in patients with cancer, showed no statistically significant differences on VrAEs in patients treated with ICI compared with participants without cancer, or patients with cancer treated with chemotherapy. Only 3 of 137 patients treated with ICI (2%) in this study had grade 3 or more VrAE. Another study showed that the patients who received ICI reported a higher increase of itch and rash after receiving the second dose of the mRNA vaccine compared with those without cancer treatment.³² However, this was reported in a conference abstract and no frequencies were provided.

This systematic review provides the most recent synthesis of evidence about the efficacy and safety of COVID-19 vaccines in patients with cancer receiving ICI. However, it had limitations inherent to the evidence that was available for review and synthesis. The certainty of the evidence in our systematic review was rated as low or very low for all the outcomes evaluated. We rated down for risk of bias and for imprecision. As we stated before, none of the studies evaluated critical outcomes (ie, mortality, several COVID-19, hospital admission). We consider seroconversion as a surrogate outcome and we rated down the certainty of evidence for indirectness.³⁸ Another limitation, is the information provided regarding to the differences in ICI, regimen, and dose and duration of ICI across the studies. Among the 16 cohort studies included, 11 (69%) did not specify the ICI used or the specific regimen (monotherapy or combination therapy). These factors might have an impact on the outcomes of interest, as it has been shown that dose and duration of ICI might affect the rate of irAE in general.³⁹ Moreover, combination therapy has a higher risk of irAE compare to monotherapy.⁴⁰ Since the primary studies of this systematic review are not randomized control trials, there are several other known and unknown confounding factors that could have an impact on the results as the compared groups may not be balanced, risk factors were not adjusted for in the analyses. Some potential confounders include demographics, prior comorbidities including history of autoimmune disorders, prior cancer treatment or concurrent medications which could impact the development of irAE.^{39–41}

In summary, the efficacy of the COVID-19 vaccination in patients with cancer treated with ICI, measured by

seroconversion, was similar to that of healthy controls and higher than that observed in patients with cancer who received chemotherapy. No increase in VrAE or irAE were reported. Our results suggest that COVID-19 vaccination seems effective and safe in patients with cancer receiving ICI, although higher-quality evidence may be needed to further establish the robustness of these findings, including observational studies with low risk of bias and evaluating clinical important outcomes of vaccination such as COVID-19 incidence and severity, and related hospitalization and mortality.

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Contributors MES-A conceived the idea of the study. MES-A and JIR developed the protocol. YG performed the literature search. JIR and MAL-O reviewed and appraised the data. JIR and MAL-O conducted the analysis. JIR, MAL-O, YG and MES-A participated in writing the manuscript.

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Competing interests The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. MES-A has received consultant fees in the past 12 months from Pfizer, Eli Lilly and Bristol Myers Squibb/Celgene unrelated to this study.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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Supplemental material**Table S1.** Ovid Medline search strategy

#	Searches
1	COVID-19.rx,px,ox. or severe acute respiratory syndrome coronavirus 2.os.
2	("COVID-19" or COVID19 or "COVID 2019" or "novel coronavirus" or "SARS-CoV" or "SARS-CoV-2" or "SARS2" or "2019-nCoV" or ncov19 or ncov-19 or "2019-novel CoV" or sarscov2 or sarscov-2 or Sars-coronavirus2 or Sars-coronavirus-2 or SARS-like coronavirus* or coronavirus-19).ti,ab,kf.
3	(coronavirus* or "corona virus*").ti,kf.
4	Coronavirus Infections/
5	or/1-4
6	20191201:20301231.(dt).
7	5 and 6 [COVID-19, SARS-COV-2]
8	limit 7 to english language
9	exp Neoplasms/
10	(cancer* or carcinom* or tumor* or tumour* or neoplas* or malignan* or metasta* or myeloma* or leuk?emia* or lymphoma* or sarcoma* or melanoma* or oncolog*).ti,ab,kf.
11	9 or 10 [Cancer]
12	8 and 11
13	(checkpoint adj3 (inhibitor* or modulator* or antibod* or block*).ti,kf, rn.
14	(checkpoint and (inhibitor* or modulator* or antibod* or block*).nm.
15	(checkpoint adj3 (inhibitor* or modulator* or antibod* or block*).ab.
16	((("cytotoxic T lymphocyte associated" adj3 "4") or "CTLA 4" or CTLA4).ti,kf, rn.
17	("Cytotoxic t-lymphocyte antigen" adj3 "4").ti,kf, rn.
18	("Cytotoxic t-lymphocyte antigen" or "cytotoxic T lymphocyte associated").nm.
19	(ipilimumab or "MDX CTLA 4" or Yervoy or "MDX 010" or MDX010 or "BMS-734016" or BMS734016).mp.
20	("Programmed Cell Death 1" or PD1 or "PD 1").ti,kf, rn, nm.

21	(pembrolizumab or Keytruda or Lambrolizumab or "Merck 3475" or Merck3475 or "MK 3475" or MK3475 or "Sch 900475" or Sch900475 or "HSDB 8257").mp.
22	(nivolumab or "BMS 936558" or BMS936558 or "MDX 1106" or MDX1106 or "ONO 4538" or ONO4538 or Opdivo).mp.
23	("AMP 514" or AMP514 or MEDI0680 or "MEDI 0680").mp.
24	("programmed death ligand 1" or "PD L1" or PDL1 or "B7-H1" or B7HI).ti,kf,tn,nm.
25	(atezolizumab or Tecentriq or MPDL3280A or "MPDL 3280A" or RO5541267 or RO-5541267 or RG 7446 or RG7446 or "CD274 ANTIGEN" or "CD274 protein").mp.
26	(durvalumab or imfinzi or "MEDI 4736" or MEDI4736).mp.
27	(avelumab or Bavencio or MSB0010718C or "MSB 0010718C" or MSB0010682).mp.
28	("BMS 936559" or BMS936559 or MDX1105 or "MDX 1105").mp.
29	(Cemiplimab or libtayo or REGN2810 or "REGN 2810").mp.
30	or/13-29
31	12 and 30 [COVID-19 + cancer patients + immunotherapy (checkpoint inhibitors)]
32	exp Vaccines/
33	exp Vaccination/
34	"vaccin*".rn,ox,px,rx.
35	vaccin*.mp.
36	((covid* or covid19 or covid-19 or SARS-COV-2 or coronavirus) and immuniz*).ti,ab,kf.
37	(Novavax or "NVX-CoV2373" or NUVAXOVID* or COVOVAX* or Moderna* or "mRNA-1273" or Pfizer* or BioNTech* or BNT162b2* or Janssen* or "Ad26.COVS.S" or AZD1222 or AstraZeneca* or Covishield or Covaxin* or "Bharat Biotech" or Sinopharm or "BBIBP-CorV" or Sinovac or CoronaVac*).mp. [WHO approved Covid-19 vaccines]
38	or/32-37 [COVID-19 vaccines]
39	31 and 38

Table S2. Ovid Embase search strategy

#	Searches
1	("COVID-19" or COVID19 or "COVID 2019" or "novel coronavirus" or "SARS-CoV" or "SARS-CoV-2" or "SARS2" or "2019-nCoV" or ncov19 or ncov-19 or "2019-novel CoV" or sarscov2 or sarscov-2 or Sars-coronavirus2 or Sars-coronavirus-2 or SARS-like coronavirus* or coronavirus-19).ti,ab,kw.
2	(coronavirus* or "corona virus*").ti.
3	severe acute respiratory syndrome/
4	coronavirus infection/
5	"coronavirus disease 2019"/
6	or/1-5
7	limit 6 to english language
8	limit 7 to dc=20191201-20221231
9	exp malignant neoplasm/
10	(cancer* or neoplas* or tumo?r* or leuk?emia* or lymphoma* or melanoma* or carcinoma* or sarcoma* or oncolog*).ti,ab,kw.
11	9 or 10
12	8 and 11
13	(immun* adj3 checkpoint adj3 (inhibitor* or modulator* or antibod* or block*).ti,hw,kw.
14	((("cytotoxic T lymphocyte associated" adj3 "4") or "CTLA 4" or CTLA4).ti,kw,hw.
15	("Cytotoxic t-lymphocyte antigen" adj3 "4").ti,kw,hw.
16	(ipilimumab or "MDX CTLA 4" or Yervoy or "MDX 010" or MDX010 or "BMS-734016" or BMS734016).ti,ab,hw,kw,du,tn.
17	("Programmed Cell Death 1" or PD1 or "PD 1").ti,kw,hw,du,tn.
18	(pembrolizumab or Keytruda or Lambrolizumab or "Merck 3475" or Merck3475 or "MK 3475" or MK3475 or "Sch 900475" or Sch900475 or "HSDB 8257").ti,ab,kw,hw,du,tn.
19	(nivolumab or "BMS 936558" or BMS936558 or "MDX 1106" or MDX1106 or "ONO 4538" or ONO4538 or Opdivo).ti,ab,kw,hw,du,tn.
20	("programmed death ligand 1" or "PD L1" or PDL1 or "B7-H1" or B7HI).ti,kw,hw.

21	(atezolizumab or Tecentriq or MPDL3280A or "MPDL 3280A" or RO5541267 or RO-5541267 or RG 7446 or RG7446 or "CD274 ANTIGEN" or "CD274 protein").ti,ab,kw,hw,du,tn.
22	(avelumab or Bavencio or MSB0010718C or "MSB 0010718C" or MSB0010682).ti,ab,kw,hw,du,tn.
23	(Cemiplimab or libtayo or REGN2810 or "REGN 2810").ti,ab,kw,hw,du,tn.
24	(durvalumab or imfinzi or "MEDI 4736" or MEDI4736).ti,ab,kw,hw,du,tn.
25	or/13-24
26	12 and 25
27	exp vaccine/
28	exp vaccination/
29	vaccin*.ti,ab,kf.
30	exp vaccination reaction/
31	vaccination refusal/
32	((covid* or covid19 or covid-19 or SARS-COV-2 or coronavirus) and immuniz*).ti,ab,kf.
33	(Novavax or "NVX-CoV2373" or NUVAXOVID* or COVOVAX* or Moderna* or "mRNA-1273" or Pfizer* or BioNTech* or BNT162b2* or Janssen* or "Ad26.COVS.S" or AZD1222 or AstraZeneca* or Covishield or Covaxin* or "Bharat Biotech" or Sinopharm or "BBIBP-CorV" or Sinovac or CoronaVac*).mp. [WHO approved Covid-19 vaccines]
34	exp immunization/
35	or/27-34
36	26 and 35

Table S3. Types of cancer and funding for each study

Study ID	Types of cancer	Funding
Agbarya 2021 ¹³	Gastrointestinal, breast, lung, urinary, gynecological, other	None
Au 2021 ¹⁴	Colorectal cancer	CAPTURE study - Royal Marsden Cancer Charity Programme
Blaise 2021 ¹⁵	Melanoma	None
Buttiron-Webber 2021 ¹⁶	Digestive, lung, breast, genitourinary and gynecologic, other.	Association WeCare and the Lions Club of Genoa Sant'Agata and the Italian Minister of Health
Chen 2021 ¹⁷	Lung cancer, melanoma, kidney cancer, gastrointestinal, hepatic cancer, head and neck, other.	NR
Di Giacomo 2021 ¹⁸	Skin cancer, thoracic malignancies, glioblastoma.	None
Figueiredo 2021 ¹⁹	Breast, gastrointestinal, melanoma, thoracic, lymphoma, leukemia, myeloma, other	NCI-funded Serological Sciences Network (SeroNet)
Lasagna 2021 ²⁰	Lung, melanoma, head and neck, bladder, breast, squamous cell skin cancer	Ricerca Corrente, Fondazione IRCCS Policlinico San Matteo, Ricerca Finalizzata, European Commission-Horizon 2020
Ligumsky 2021 ²¹	Gastrointestinal, breast, gynecological, genitourinary, skin cancer, melanoma, central nervous system, sarcoma, head and neck, non-small cell lung cancer	None
Ma 2021 ²²	Head and neck, gastrointestinal, non-small cell lung cancer	Guangdong science and technology special fund mayor project and Shantou City Science and Technology Plan Project and 2020 Li Ka Shing Foundation Cross-Disciplinary Research Grant and the Fellowship of China Postdoctoral Science Foundation and National Natural Science Foundation of China Youth Science Fund Project and National Natural Science Foundation of China Youth Science Fund Project
Massarweh 2021 ²³	Gastrointestinal, lung, breast, brain, genitourinary, other.	NR
Mieczkowska 2021 ²⁴	Hepatocellular carcinoma	NR
Naranbhai 2021 ⁴²	Thoracic cancer, breast, melanoma, Merkel cell cancer, head and neck, gastrointestinal, leukemia, lymphoma, myeloproliferative neoplasm or myelodysplastic syndrome	Lambertus Family Foundation
Oosting 2021 (VOICE trial) ²⁶	Bone or soft tissue, breast, central nervous system, digestive tract, endocrine glands, female genital organs, head and neck, male genital organs, respiratory tract, skin, urinary tract, other.	The Netherlands Organization for Health Research and Development
Strobel 2021 ²⁷	Skin cancer	Projekt DEAL

Subbiah 2021 ³²	Breast, genitourinary, thoracic, hematologic, head and neck, colorectal cancer.	American Cancer Society, the Andrew Sabin Family Foundation, Gabrielle's Angels Foundation, Cancer and Aging Research Group (CARG) R21/R33 Infrastructure Grant, Gabrielle's Angel Foundation For Cancer Research U.S. National Institutes of Health
Svoboda 2021 ²⁹	<i>Hodgkin lymphoma</i>	NR
Thakkar 2021 ³⁰	Breast, gastrointestinal, genitourinary, gynecological, thoracic, head and neck, skin, musculoskeletal, carcinoma of unknown primary, lymphoid malignancy, myeloid malignancy, plasma cell malignancy	NR
Waissengrin 2021 ³¹	Lung, genitourinary, gastrointestinal, melanoma, others	None

NA=not applicable; NR=not reported; ICI=immune checkpoint inhibitor; PD-1= programmed cell death 1; PD-L1=programmed cell death ligand 1; ^apatients' relatives, health-care workers, and volunteers, ^bIncludes patients receiving other treatments plus ICI

Table S4. Results of individual cohort studies

Study ID	ICI Events/Total (%)	Chemotherapy events/total (%)	Cancer patients with no active treatment Events/Total (%)	Individuals without cancer Events/Total (%)	Comments
Seroconversion					
Agbarya 2021	23/26 (88.5)	57/70 (81.4)	-	25/26 (96.2)	-
Buttiron Webber 2021	20/21 (95.2)	92/115 (80)	61/62 (98.4)	-	-
Di Giacomo 2021	69/70 (98.6)	13/28 (46.4)	-	42/42 (100)	-
Figueiredo 2021	27/29 (93.1)	26/26 (100)	13/13 (100)	-	-
Lasagna 2021	68/88 (77)	-	-	-	-
Ligumsky 2021	50/55 (90.9)	82/101 (81.2)	-	159/164 (96.9)	-
Ma 2021	94/138 (68.1)	-	-	111/138 (80.4)	Sinovac and Sinopharm
Massarweh 2021	22/22 (100)	28/30 (93.3)	-	78/78 (100)	-
Naranbhai 2021	53/54 (98.1)	73/77 (94.8)	148/153 (96.7)	-	-
Oosting 2021	130/131 (99.2)	223/229 (97.4)	-	240/240 (100)	-
Svoboda 2021	11/12 (92)	-	-	-	-
Thakkar 2021	30/31 (96.8)	90/102 (88.2)	-	55/59 (93.2)	-
Immune related adverse events					
Lasagna 2021	1/88 (1.1)	-	-	-	1 patient had colitis and hepatitis grade 3

Ma 2021	Pneumonitis: vaccinated 7/127 (5.5) vs no vaccinated 8/127 (6.3) Rash: vaccinated 30/127 (23.6) vs no vaccinated 29/127 (22.8) Arthralgia: vaccinated 17/127 (13.4) vs no vaccinated 18/127 (14.2) Liver function test: vaccinated 16/127 (12.6) vs no vaccinated 15/127 (15.8) Diarrhea: vaccinated 9/127 (7.1) vs no vaccinated 11/127 (8.7)	-	-	-	
Chen 2021	0/84	-	-	-	-
Oosting 2021	13/300 (4.3) ^a	-	-	-	Most low grade. 1 died from pneumonitis, 1 grade 3 adrenal insufficiency, 1 grade 3 thrombocytopenia
Strobel 2021	15/85 (17)				8 patients grade 3: 3 colitis, 1 hepatitis, 2 myositis, 1 myocarditis, 1 both colitis and thyroiditis.
Waissengrin 2021	0/134				
Vaccine related adverse events					
Naranbhai 2021	-	-	-	-	All cancer patients: 507/671 (75.6%) local or systemic. 89% mild or moderate
Oosting 2021	Fatigue: 78/132 (59)	111/227 (48.9)	-	129/238 (54.2)	-
	Pain: 8/132 (6)	11/227 (5)	-	9/238 (4)	-
	Grade 3 or worse: 3/137 (2)	6/244 (2)	-	0/240	-
Strobel 2021	Moderate pain 24/85 (40) Fatigue 20/85 (24)	-	-	-	-
Lasagna 2021	24/88 (27.3)	-	-	-	22 had pain at site of injection, 2 fever

Ligumsky 2021	-	-	-	-	183/326 (56.1%). Local pain: 19.6%; weakness: 17.5%; myalgia: 12.6%; headache: 6.4%
Ma 2021	Rash: 35/134 (26.1)	-	-	-	No ICI. Rash 10/134 (7.5%)
Buttiron Webber 2021	-	-	-	-	Cancer patients on active treatment (all treatments): 43/291 (14.8%), mostly mild or moderate
Subbiah 2021	-	-	-	-	Patients with prior ICI had higher increase in itch and rash from their baseline vs patients without systemic treatment (p < 0.05).
Svoboda 2021	Pain: 7/12 (58) Fatigue: 5/12 (42)	-	-	-	All adverse events were grade 1 or 2
Waissengrin 2021	Pain: 85/134 (63) Fatigue: 45/134 (34)	-	-	-	None of them required admission to hospital or any other special intervention

^aincludes patients who received chemoimmunotherapy; ICI=immune checkpoint inhibitors

Table S5. Risk of bias of studies included for analysis

Author	Selection				Comparability		Outcome			Total score
	Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study, OR baseline assessment	Adjust for the most important risk factors	Adjust for other risk factors	Assessment of outcome	Follow-up length	Loss to follow-up rate	
☆☆ Agbarya 2021 ⁱ										3
☆☆ Butiron Webber 2021										5
☆☆ Chen 2021										3
☆☆☆☆ Di Giacomo 2021										5
☆☆☆☆ Figueiredo 2021										7
☆☆☆☆ Lasagna 2021		NA								4
☆☆ Ligumsky 2021										3
☆☆☆☆ Ma 2021										8
☆☆ Massarweh 2021										5
☆☆☆☆ Naranbhai 2022										8
☆☆☆☆ Oosting 2021										8
☆☆ Strobel 2021										3
☆☆☆☆ Subbiah 2021										6
☆☆ Svoboda 2021										3
☆☆ Thakkar 2021										4
☆☆ Waissengrin 2021										4

ⁱCross-sectional study for which we only assessed the domains not related to cohort studies

Table S6. Summary of findings table for the comparison: cancer patients treated with ICI versus individuals without cancer**Safety and efficacy of COVID-19 vaccination in cancer patients treated with ICI compared with individuals without cancer****Patient or population:** patients who received COVID-19 vaccine**Setting:** outpatient**Intervention:** ICI**Comparison:** individuals without cancer

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with individuals without cancer	Risk with ICI				
COVID-19 infection, Severe COVID-19, COVID-19 mortality	Not reported					
Seroconversion assessed with: Proportion of patients' seroconversion: follow-up: median 30 days	950 per 1,000	922 per 1,000 (874 to 979)	RR 0.97 (0.92 to 1.03)	1237 (5 observational studies)	⊕○○○ Very low ^{a,b,c}	We are uncertain whether cancer patients treated with ICI have a lower seroconversion rate after the COVID-19 vaccination compared with individuals without cancer

CI=confidence interval; RR= risk ratio; ICI=immune checkpoint inhibitor; GRADE=Grading of Recommendations, Assessment, Development and Evaluations

Explanations

- Representativeness of exposed cohort and the adjustment for risk factors were the important items that were not accomplished in most of studies
- The true effect could either benefit or harm the patient
- Seroconversion is considered a surrogate outcome and we rated down for indirectness

Table S7. Summary of findings for the comparison: cancer patients treated with ICI versus cancer patients without active treatment**Safety and efficacy of COVID-19 vaccination in cancer patients treated with ICI compared with cancer patients without active treatment****Safety and efficacy of COVID-19 vaccination in cancer patients treated with ICI compared with cancer patients treated with chemotherapy****Patient or population:** patients who receive COVID-19 vaccine**Setting:** outpatient**Intervention:** ICI**Comparison:** no active treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no active treatment	Risk with ICI				
COVID-19 infection, Severe COVID-19, COVID-19 mortality	Not reported					
Seroconversion follow-up: median 30 days	974 per 1,000	974 per 1,000 (935 to 1,000)	RR 1.00 (0.96 to 1.04)	332 (3 observational studies)	⊕○○○ Very low ^{a,b,c}	We are uncertain whether cancer patients treated with ICI have a higher seroconversion rate after the COVID-19 vaccination compared with cancer patients without active treatment

CI=confidence interval; RR= risk ratio; ICI=immune checkpoint inhibitor; GRADE=Grading of Recommendations, Assessment, Development and Evaluations

Explanations

a. Representativeness of exposed cohort and the adjustment for risk factors were the important items that were not accomplished in most of studies

b. The true effect could either benefit or harm the patient

c. Seroconversion is considered a surrogate outcome and we rated down for indirectness

Patient or population: Patients who receive COVID-19 vaccine
Setting: outpatient
Intervention: ICI
Comparison: chemotherapy

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Chemotherapy	Risk with ICI				
COVID-19 infection, Severe COVID-19, COVID-19 mortality, follow-up: median 10 weeks	No events were reported		-	(3 observational studies)	⊕○○○ Very low ^{a,b}	-
Seroconversion assessed with: Proportion of patients with seroconversion: follow-up: median 30 days	879 per 1,000	958 per 1,000 (879 to 1,000)	RR 1.09 (1.00 to 1.18)	1217 (9 observational studies)	⊕○○○ Very low ^{a,b,c}	We are uncertain whether cancer patients treated with ICI have a higher seroconversion rate after the COVID-19 vaccination compared with cancer patients treated with chemotherapy
Vaccine related adverse events (grade 3 or more): follow- up: median 30 days	8 per 1,000	8 per 1,000 (2 to 29)	RR 0.98 (0.23 to 3.50)	381 (1 study)	⊕○○○ Very Low ^d	We are uncertain whether cancer patients treated with ICI have lower risk of grade 3 or more VrAE after mRNA vaccination compared to cancer patients treated with chemotherapy

CI=confidence interval; RR= risk ratio; ICI=immune checkpoint inhibitor; GRADE=Grading of Recommendations, Assessment, Development and Evaluations

Explanations

a. Representativeness of exposed cohort and the adjustment for risk factors were the important items that were not accomplished in most of studies

b. The true effect could either benefit or harm the patient

c. Seroconversion is considered a surrogate outcome and we rated down for indirectness

d. Low number of events and the true effect could either benefit or harm the patient

Table S8. Summary of findings for the comparison: cancer patients treated with ICI versus cancer patients treated with chemotherapy

Table S9. Excluded studies

Study ID	Reference	Reason for exclusion
Aalberg 2021	Aalberg JJ, Collins TP, Dobrow EM. Axillary lymphadenopathy in a renal cell carcinoma patient after COVID-19 Vaccination. <i>Radiol Case Rep.</i> 2021 Aug;16(8):2164-2167. doi: 10.1016/j.radcr.2021.05.031. Epub 2021 Jun 11. PMID: 34149984; PMCID: PMC8194501.	Outcome: not unusual adverse event
Brest 2021	Brest P, Mograbi B, Hofman P, Milano G. COVID-19 vaccination and cancer immunotherapy: should they stick together? <i>Br J Cancer.</i> 2022 Jan;126(1):1-3. doi: 10.1038/s41416-021-01618-0. Epub 2021 Nov 19. PMID: 34799696; PMCID: PMC8603902.	Study design
Da Cruz 2021	Tomas TD, Eiriz IF, Vitorino M, Vicente RS, Mendes AD, Sousa MS, Braga S, Fiuza TM, Gonçalves LA, Gonçalves CP, Demengeot J. 1602P COVID-19 vaccination efficacy in cancer patients: An ongoing prospective trial. <i>Annals of Oncology.</i> 2021 Sep 1;32:S1147.	Intervention: no ICI
Gauci 2021	Gauci ML, Coutzac C, Houot R, Marabelle A, Lebbé C; FITC. SARS-CoV-2 vaccines for cancer patients treated with immunotherapies: Recommendations from the French society for Immunotherapy of Cancer (FITC). <i>Eur J Cancer.</i> 2021 May;148:121-123. doi: 10.1016/j.ejca.2021.02.003. Epub 2021 Feb 18. PMID: 33743480; PMCID: PMC7891073.	Wrong study design
Gomez 2021	Gomez J, Krammer F, Mack P, Rolfo C, Rohs N, Moore A, King J, Henschke C, Yankelevitz D, Shyr Y, Taioli E. Analysis of lung cancer patients receiving SARS-CoV-2 vaccines revealed a minority subset with poor antibody responses relative to controls. <i>Journal of Thoracic Oncology.</i> 2021:S848-.	Intervention: data for ICI not reported separated
Hughes 2021	Hughes NM, Hammer MM, Awad MM, Jacene HA. Radiation Recall Pneumonitis on FDG PET/CT Triggered by COVID-19 Vaccination. <i>Clin Nucl Med.</i> 2022 Mar 1;47(3):e281-e283. doi: 10.1097/RLU.0000000000003980. PMID: 34739397; PMCID: PMC8820752.	Outcome: any adverse event
Hwang 2021	Hwang JK, Zhang T, Wang AZ, Li Z. COVID-19 vaccines for patients with cancer: benefits likely outweigh risks. <i>J Hematol Oncol.</i> 2021 Feb 27;14(1):38. doi: 10.1186/s13045-021-01046-w. PMID: 33640005; PMCID: PMC7910769.	Wrong study design
Karacin 2021	Karacin C, Eren T, Zeynelgil E, Imamoglu GI, Altinbas M, Karadag I, Basal FB, Bilgetekin I, Sutcuoglu O, Yazici O, Ozdemir N, Ozet A, Yildiz Y, Esen SA, Ucar G, Uncu D, Dinc B, Aykan MB, Erturk İ, Karadurmus N, Civelek B, Çelik İ, Ergun Y, Dogan M, Oksuzoglu OB. Immunogenicity and safety of the CoronaVac vaccine in patients with cancer receiving active systemic therapy. <i>Future Oncol.</i> 2021 Nov;17(33):4447-4456. doi: 10.2217/fo-2021-0597. Epub 2021 Aug 3. PMID: 34342517; PMCID: PMC8336634.	Intervention: less than 3 patients on ICI
Lasagna 2021	AIOM abstracts. <i>Tumori Journal.</i> 2021;107(2_suppl):1-188. doi:10.1177/03008916211041664	Congress abstract: results are the same for Lasagna 2021

Lasagna 2022	Lasagna A, Lilleri D, Agustoni F, Percivalle E, Borgetto S, Alessio N, Comolli G, Sarasini A, Bergami F, Sammartino JC, Ferrari A, Zavaglio F, Arena F, Secondino S, Falzoni M, Schiavo R, Lo Cascio G, Cavanna L, Baldanti F, Pedrazzoli P, Cassaniti I. Analysis of the humoral and cellular immune response after a full course of BNT162b2 anti-SARS-CoV-2 vaccine in cancer patients treated with PD-1/PD-L1 inhibitors with or without chemotherapy: an update after 6 months of follow-up. <i>ESMO Open</i> . 2022 Feb;7(1):100359. doi: 10.1016/j.esmoop.2021.100359. Epub 2021 Dec 11. PMID: 34973510; PMCID: PMC8664661.	Outcome: humoral response at 6 months follow-up
Luo 2021	Luo B, Li J, Hou X, Yang Q, Zhou Y, Ye J, Wu X, Feng Y, Hu T, Xu Z, He Y, Sun J. Indications for and contraindications of immune checkpoint inhibitors in cancer patients with COVID-19 vaccination. <i>Future Oncol</i> . 2021 Sep;17(26):3477-3484. doi: 10.2217/fon-2021-0288. Epub 2021 Jun 30. PMID: 34189948; PMCID: PMC8244550.	Study design
Malek 2022	Malek AE, Cornejo PP, Daoud N, Alam M. The mRNA COVID-19 vaccine in patients with cancer receiving checkpoint inhibitor therapy: what we know and what we don't. <i>Immunotherapy</i> . 2022 Feb;14(2):91-94. doi: 10.2217/imt-2021-0235. Epub 2021 Nov 8. PMID: 34747190; PMCID: PMC8582594.	Study design
Malissen 2021	Malissen N, Ninove L, de Lamballerie X, André N, Gaudy-Marqueste C. Safety and immunogenicity after 2 doses of the BNT162b2 COVID-19 vaccine in an early-phase oncology trial centre population. <i>Eur J Cancer</i> . 2021 Oct;156:125-126. doi: 10.1016/j.ejca.2021.07.040. Epub 2021 Aug 10. PMID: 34438245; PMCID: PMC8352671.	Intervention: data for ICI not reported separated
Monin 2021	Monin L, Laing AG, Muñoz-Ruiz M, McKenzie DR, Del Molino Del Barrio I, Alaguthurai T, Domingo-Vila C, Hayday TS, Graham C, Seow J, Abdul-Jawad S, Kamdar S, Harvey-Jones E, Graham R, Cooper J, Khan M, Vidler J, Kakkassery H, Sinha S, Davis R, Dupont L, Francos Quijorna I, O'Brien-Gore C, Lee PL, Eum J, Conde Poole M, Joseph M, Davies D, Wu Y, Swampillai A, North BV, Montes A, Harries M, Rigg A, Spicer J, Malim MH, Fields P, Patten P, Di Rosa F, Papa S, Tree T, Doores KJ, Hayday AC, Irshad S. 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. <i>Lancet Oncol</i> . 2021 Jun;22(6):765-778. doi: 10.1016/S1470-2045(21)00213-8. Epub 2021 Apr 27. PMID: 33930323; PMCID: PMC8078907.	Intervention: outcomes measure after first dose in patients treated with ICI
Saini 2021	Saini KS, Martins-Branco D, Tagliamento M, Vidal L, Singh N, Punie K, Saini ML, Chico I, Curigliano G, de Azambuja E, Lambertini M. Emerging issues related to COVID-19 vaccination in patients with cancer. <i>Oncol Ther</i> . 2021 Dec;9(2):255-265. doi: 10.1007/s40487-021-00157-1. Epub 2021 Jun 16. PMID: 34137014; PMCID: PMC8208766.	Study design
Terpos 2021	Terpos E, Zagouri F, Lontos M, Sklirou AD, Koutsoukos K, Markellos C, Briasoulis A, Papanagnou ED, Trougakos IP, Dimopoulos MA. Low titers of SARS-CoV-2 neutralizing antibodies after first vaccination dose in cancer patients receiving checkpoint inhibitors. <i>J Hematol Oncol</i> . 2021 May 31;14(1):86. doi: 10.1186/s13045-021-01099-x. PMID: 34059088; PMCID: PMC8165511.	Intervention: 1 dose of the vaccine

Tougeron 2021	Tougeron D, Hentzien M, Seitz-Polski B, Bani-Sadr F, Bourhis J, Ducreux M, Gaujoux S, Gorphe P, Guiu B, Hoang-Xuan K, Huguet F, Lecomte T, Lièvre A, Louvet C, Maggiori L, Mansi L, Mariani P, Michel P, Servettaz A, Thariat J, Westeel V, Aparicio T, Blay JY, Bouché O; for Thésaurus National de Cancérologie Digestive (TNCD); réseau de Groupes Coopérateurs en Oncologie (GCO); Fédération Nationale des Centres de Lutte Contre le Cancer (UNICANCER); Association de Chirurgie Hépatobiliaire-Pancréatique et Transplantation (ACHBT); Association de Recherche sur les Cancers Gynécologiques-Groupes d'Investigateurs Nationaux pour l'étude des Cancers Ovariens et du Sein (ARCAGY-GINECO); Fédération Francophone de Cancérologie Digestive (FFCD); Groupe Coopérateur multidisciplinaire en Oncologie (GERCOR); Groupe d'Oncologie Radiothérapie Tête et Cou-Intergroupe ORL (GORTEC-Intergroupe ORL); Intergroupe Francophone de Cancérologie Thoracique (IFCT); InterGroupe Coopérateur de Neuro-Oncologie/Association des Neuro-Oncologues d'Expression Française (IGCNO-ANOCEF); Société Française de Chirurgie Digestive (SFCD); Société Française d'Endoscopie Digestive (SFED); Société Française de Radiothérapie Oncologique (SFRO); Société Française de Radiologie (SFR); Société Nationale Française de Colo-Proctologie (SNFCP); Société Nationale Française de Gastroentérologie (SNFGE). Severe acute respiratory syndrome coronavirus 2 vaccination for patients with solid cancer: Review and point of view of a French oncology intergroup (GCO, TNCD, UNICANCER). <i>Eur J Cancer</i> . 2021 Jun;150:232-239. doi: 10.1016/j.ejca.2021.03.030. Epub 2021 Apr 1. PMID: 33934060; PMCID: PMC8015403.	Study design
Yedekuz 2021	mRNA-based COVID-19 vaccines appear not to increase immune events in cancer patients receiving immune checkpoint inhibitors	Study design

ICI=immune checkpoint inhibitor