IN VIVO 40: 2476-2488 (2026)
doi: 10.21873/invivo.14401

Impact of COVID-19 Vaccine Type on the Efficacy and Safety of Nivolumab in Patients With Metastatic Non-small-cell Lung Cancer: A Multicenter Study

BERKAN KARABUGA[1], MUSTAFA BÜYÜKKÖR[1], CENGIZ KARAÇIN[1], EKIN KONCA KARABUGA[2], SEDAT YILDIZ[3], GÖKÇE GÜL GÜNEYSU[4], GÜNER AKGÜNER[2], FATMA KESKIN UZUNDERE[5], AYŞE ARSLAN[6], SENA ECE DAVARCI[3], ZUHAT URAKÇI[5], OSMAN SÜTÇÜOĞLU[6], ÖZGEN AHMET YILDIRIM[2], NURI KARADURMUŞ[4] and YAKUP ERGÜN[7,8]

[1]Department of Medical Oncology, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Ankara, Türkiye;
[2]Department of Medical Oncology, Ankara Etlik City Hospital, Ankara, Türkiye;
[3]Department of Medical Oncology, Afyonkarahisar Health Sciences University, Afyonkarahisar, Türkiye;
[4]Department of Medical Oncology, Gülhane Training and Research Hospital, Ankara, Türkiye;
[5]Department of Medical Oncology, Dicle University Faculty of Medicine, Diyarbakır, Türkiye;
[6]Department of Medical Oncology, Gazi University Faculty of Medicine, Ankara, Türkiye;
[7]Department of Medical Oncology, Bower Hospital, Diyarbakır, Türkiye;
[8]Vocational School of Health Services, Istanbul Kent University, Istanbul, Türkiye

Abstract

Background/Aim: The effect of COVID-19 vaccine type on the outcomes of therapy immune checkpoint inhibitors remains unclear, and concerns persist regarding whether mRNA-based vaccines may negatively impact treatment efficacy or increase immune-related toxicity. This study aimed to evaluate the association between COVID-19 vaccination type and the efficacy and safety of nivolumab in patients with metastatic non-small-cell lung cancer (NSCLC).

Patients and Methods: We retrospectively analyzed 138 patients with driver-negative metastatic NSCLC treated with second-line nivolumab. Patients were classified as receiving virion-based (Sinovac) only, mRNA-based only, or both types of vaccines. Treatment response, progression-free survival, objective response rate, clinical benefit rate clinical benefit rate and immune-related adverse events were compared.

Results: The overall response and clinical benefit rates were similar across vaccination groups, with no significant differences observed (p=0.38 and p=0.16, respectively). Median progression-free survival did not differ significantly

continued

Berkan Karabuğa, Department of Medical Oncology, Dr. Abdurrahman Yurtaslan Ankara Oncology Research and Training Hospital, Ankara, Türkiye. Tel: +90 5378563905, e-mail: berkan.karabuga@saglik.gov.tr, drbkarabuga@gmail.com

Received March 10, 2026 | Revised April 15, 2026 | Accepted April 16, 2026

among the different groups (p=0.39). The incidence of any-grade and grade 3-4 immune-related adverse events was comparable across groups, although grade 1-2 immune-related adverse events were more frequent among patients who had received at least one dose of Sinovac.

Conclusion: In patients with metastatic NSCLC receiving second-line nivolumab, the efficacy and safety profile of nivolumab did not differ according to the type of COVID-19 vaccine patients had received prior to therapy.

Keywords: Covid-19, virion-based, mRNA-based, nivolumab, lung cancer.

Introduction

The COVID-19 pandemic profoundly disrupted cancer care worldwide, leading to delays in diagnosis, interruptions in systemic therapy, and reduced access to routine follow-up, particularly for patients with advanced malignancies (1, 2). Patients with cancer were shown to have a higher risk of severe COVID-19 and mortality, largely due to immunosuppression related to both the disease and anticancer treatments (3). Consequently, COVID-19 vaccination rapidly became a cornerstone of supportive care in oncology.

Multiple vaccine platforms, including inactivated virion-based and mRNA-based vaccines, were widely implemented and demonstrated substantial effectiveness in reducing severe COVID-19, hospitalization, and death among patients with cancer (4). However, given the immune-modulating properties of both types of COVID-19 vaccine and immune checkpoint inhibitors (ICIs), concerns emerged regarding potential interactions, particularly whether vaccination alter treatment efficacy or increase immune-related adverse events (irAEs) (5). Although early real-world studies suggested that COVID-19 vaccination is generally safe in patients receiving ICIs, most reports evaluated vaccination status as a binary variable and did not explore the potential differential impact of specific vaccine platforms [reviewed in (6)].

In metastatic, driver mutation-negative non-small-cell lung cancer (NSCLC), nivolumab is a standard second-line treatment based on its demonstrated survival benefit (7). Given the immune-modulating nature of programmed cell death protein 1 (PD1) blockade, it has been hypothesized that vaccine-induced immune activation might influence antitumor immunity (8). Supporting this concept, a recent analysis from MD Anderson Cancer Center including 180 patients reported that SARS-CoV-2 mRNA vaccination sensitized tumors to immune checkpoint blockade and modulated the tumor immune microenvironment (9).

Against this background, as far as we are aware, no study to date has directly compared the long-term effects of globally administered virion-based and mRNA-based COVID-19 vaccines given well before ICI initiation on clinical outcomes in patients receiving ICIs. Most prior analyses focused on vaccinations administered shortly before or during immunotherapy, typically within a few months of treatment initiation. Therefore, we conducted a multicenter retrospective study to investigate whether COVID-19 vaccination type administered at least 6 months prior to nivolumab initiation influences treatment response, progression-free survival (PFS), and safety in patients with driver mutation-negative metastatic NSCLC treated with second-line nivolumab. We aimed to provide real-world evidence on the potential long-term immunological impact of different COVID-19 vaccine platforms on the efficacy and safety of PD1 blockade and to clarify whether these vaccines exert any detrimental effects on long-term patient outcomes.

Patients and Methods

This multicenter retrospective study included patients with driver mutation-negative metastatic NSCLC who received second-line nivolumab between 2021 and 2024 across seven centers. Eligible patients were required to have received at least one dose of a COVID-19 vaccine at any time prior to nivolumab initiation and to have a minimum interval of 6 months between the most recent vaccine dose and the start of nivolumab therapy. Patients treated exclusively with nivolumab were included to ensure treatment homogeneity and because nivolumab is the only ICI reimbursed for second-line treatment of metastatic NSCLC under national healthcare policies in our country. Inclusion criteria were age ≥18 years, histologically confirmed metastatic NSCLC, absence of actionable driver mutations, treatment with nivolumab in the second-line setting, receipt of at least one dose of a COVID-19 vaccine, and availability of clinical outcome and toxicity data. Exclusion criteria were prior treatment with ICIs, nivolumab administered in lines other than second-line, initiation of nivolumab within 6 months of COVID-19 vaccination, incomplete vaccination or follow-up data, and presence of known driver mutations.

Patients were categorized according to COVID-19 vaccination type into three groups: Virion-based vaccine only (Sinovac), mRNA-based vaccine only, and both vaccine types (at least one dose of Sinovac and at least one dose of an mRNA vaccine). Additional subgroup analyses were performed by stratifying patients according to receipt of at least one dose of an mRNA-based vaccine (yes *vs.* no), receipt of at least one dose of a virion-based vaccine (yes *vs.* no), and receipt of both vaccine types (yes *vs.* no).

The objective response rate (ORR) was defined as the proportion of patients who achieved a complete or partial response as their best overall response to nivolumab, and the clinical benefit rate (CBR) was defined as the proportion of patients who achieved complete or partial response, or stable disease. PFS was defined as the time from nivolumab initiation to documented disease progression or death from any cause, whichever occurred first, and patients without progression or death at the time of analysis were censored at the date of last follow-up. Treatment response was assessed according to the Response Evaluation Criteria in Solid Tumors, version 1.1 (10).

irAEs were recorded and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0 (11), and categorized as grade 1-2 (mild to moderate) or grade 3-4 (severe). The incidence of any-grade, grade 1-2, and grade 3-4 irAEs was compared across vaccination groups, and organ-specific irAE distributions were also analyzed.

Categorical variables were summarized as frequencies and percentages and compared using the chi-square test or Fisher's exact test, as appropriate. Continuous variables were summarized as medians (range) and compared using the Mann-Whitney *U*-test or Kruskal-Wallis test, as appropriate. PFS was estimated using the Kaplan-Meier method, and differences between groups were compared using the log-rank test. Subgroup analyses were performed according to vaccine type (Sinovac *vs.* mRNA *vs.* both), receipt of at least one dose of an mRNA vaccine (yes *vs.* no), receipt of at least one dose of a virion-based vaccine (yes *vs.* no), and receipt of both vaccine types (yes *vs.* no). Because age distribution differed among vaccination groups, an additional age-stratified PFS analysis (<65 *vs.* ≥65 years) was conducted to evaluate the potential confounding effect of age. All statistical analyses were performed using IBM SPSS Statistics, version 27.0 (IBM Corp., Armonk, NY, USA), and a two-sided *p*-value of <0.05 was considered statistically significant.

Statement of ethics. This study was approved by the Non-Interventional Ethics Committee of Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital (Approval No.: 2026-02/15).

Results

A total of 138 patients with driver-negative metastatic NSCLC who received second-line nivolumab across seven centers were included. The median follow-up time was 25.3 months. Patients were grouped according to COVID-19 vaccination status as virion-based (Sinovac) only (26.1%), mRNA-based only (32.6%), or both types (41.3%). The minimum interval between vaccination and nivolumab initiation was 6 months by design. Baseline clinicopathological characteristics are summarized in Table I. Apart from the age distribution, baseline characteristics were well balanced among the

Table I. *Clinicopathological and demographical features of patients overall and according to COVID-19 vaccine type.*

Factor	Subgroup	Virion-based (Sinovac), n (%)	mRNA-based, n (%)	Both, n (%)	*p*-Value
Age	<65 Years	17 (47.2)	30 (66.7)	23 (40.4)	**0.03**
	≥65 Years	19 (52.8)	15 (33.3)	34 (59.6)	
Sex	Female	2 (5.6)	5 (11.1)	8 (14)	0.44
	Male	34 (94.4)	40 (88.9)	49 (86)	
Comorbidity	<2	22 (61.1)	31 (68.9)	35 (61.4)	0.68
	≥2	14 (38.9)	14 (31.1)	22 (38.6)	
ECOG PS	0	10 (27.8)	18 (40)	23 (40.4)	0.41
	1	26 (72.2)	27 (60)	34 (59.6)	
Stage at time of diagnosis	Early/locally advanced	17 (47.2)	18 (40)	25 (43.9)	0.81
	Metastatic	19 (52.8)	27 (60)	32 (56.1)	
NSCLC subtype	Adenocarcinoma	20 (55.6)	29 (64.4)	36 (63.2)	0.68
	SCC	16 (44.4)	16 (35.6)	21 (36.8)	
Brain metastasis	No	26 (72.2)	31 (68.9)	34 (59.6)	0.40
	Yes	10 (27.8)	14 (31.1)	23 (40.4)	
Liver metastasis	No	32 (88.9)	39 (86.7)	45 (78.9)	0.37
	Yes	4 (11.1)	6 (13.3)	12 (21.1)	
PD-L1 level	0%	23 (62.2)	26 (57.8)	31 (55.4)	0.05
	1-49%	11 (29.7)	14 (31.1)	9 (16.1)	
	>50%	3 (8.1)	5 (11.1)	16 (28.5)	

ECOG PS: Eastern Cooperative Oncology Group performance score; NSCLC: non small-cell lung cancer; PD-L1 programmed cell death 1 protein ligand 1; SCC: squamous cell carcinoma. Statistically significant *p*-values are shown in bold.

vaccination groups. Because age differed significantly across groups, an age-stratified PFS analysis (<65 *vs.* ≥65 years) was performed and showed no significant difference in median PFS (*p*=0.07).

Treatment response. The ORR for the entire cohort was 45.7% and did not differ significantly according to vaccine type (Sinovac 52.8%, mRNA-based 37.8%, both types 47.4%; *p*=0.38). Similarly, no significant differences were observed when patients were stratified by receipt of at least one dose of mRNA vaccine (43.1% *vs.* 52.8%, *p*=0.31), at least one dose of Sinovac (49.5% *vs.* 37.8%, *p*=0.19), or both types (47.4% *vs.* 44.4%, *p*=0.73) (Table II).

The CBR for the entire cohort was 85.5% and also comparable across vaccination groups (Sinovac 86.1%, mRNA-based 77.8%, both types 91.2%; *p*=0.16). No significant differences were observed between patients who did or did not receive at least one dose of mRNA-based vaccine (85.3% *vs.* 86.1%, *p*=0.91), at least one dose of Sinovac (89.2% *vs.* 77.8%, *p*=0.07), or both (91.2% *vs.* 81.5%, *p*=0.11).

Table II. *Treatment response rates according to vaccine type.*

		ORR, %	*p*-Value	CBR, %	*p*-Value
Vaccine type	mRNA-based	37.8	0.38	77.8	0.16
	Virion-based	52.8		86.1	
	Both	47.4		91.2	
At least one mRNA-based dose	Yes	43.1	0.31	85.3	0.91
	No	52.8		86.1	
At least one virion-based dose	Yes	49.5	0.19	89.2	0.07
	No	37.8		77.8	
Both types	Yes	47.4	0.73	91.2	0.11
	No	44.4		81.5	

CBR: Clinical benefit rate; ORR: overall response rate.

Progression-free survival. Median PFS for the overall cohort was 25.3 months. According to vaccine type, median PFS was 22.9 months for patients who received virion-based (Sinovac) vaccine only, 18.7 months for those who received mRNA-based vaccines only, and 25.3 months for those who received both vaccine types (*p*=0.39) (Figure 1). Similarly,

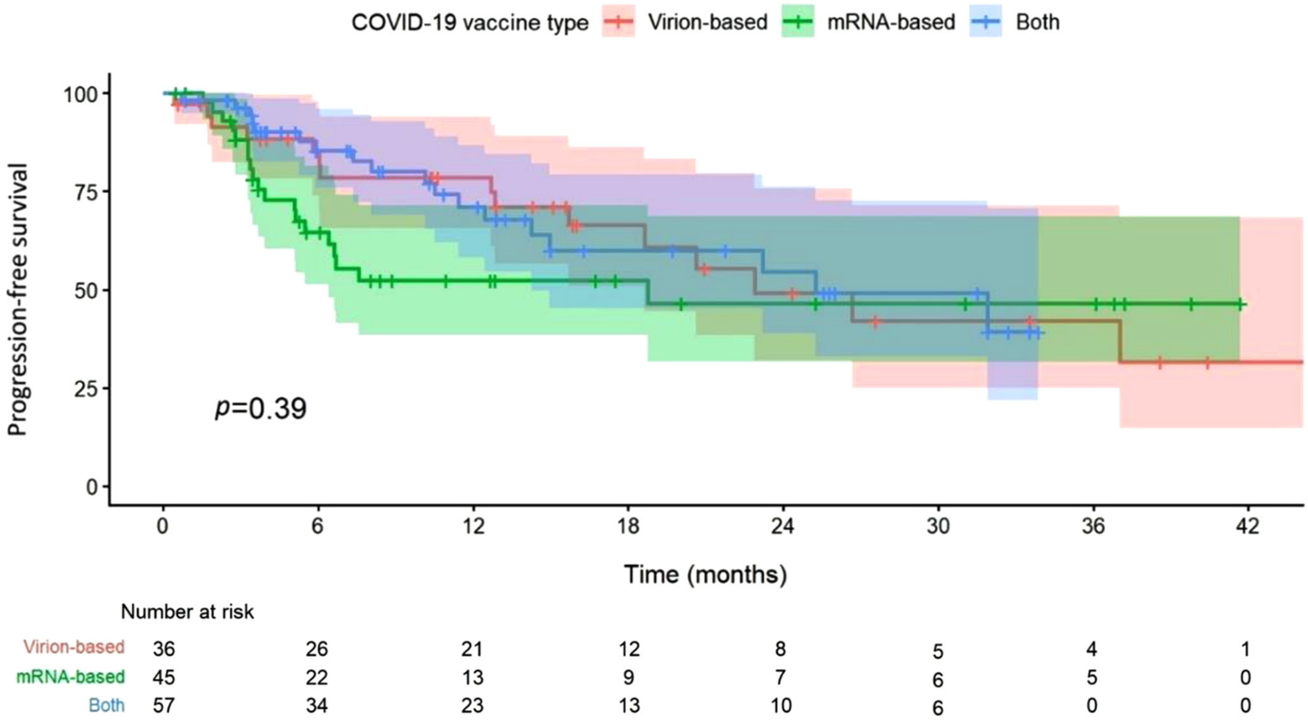

Figure 1. *Progression-free survival according to COVID-19 vaccine type.*

no significant differences in median PFS were observed in subgroup analyses according to receipt of at least one dose of an mRNA vaccine (25.3 *vs.* 22.9 months, *p*=0.69), at least one dose of a virion-based vaccine (25.3 *vs.* 18.7 months, *p*=0.18), or both vaccine types (25.3 *vs.* 20.6 months, *p*=0.39) (Figure 2, Figure 3 and Figure 4).

Safety analysis. The incidence of any-grade irAEs did not differ significantly according to vaccine type (Sinovac 27.8%, mRNA-based 17.8%, both types 33.3%; *p*=0.21). Similarly, no significant differences were observed between patients who did or did not receive at least one dose of mRNA-based vaccine (26.5% *vs.* 27.8%, *p*=0.88), at least one dose of Sinovac (31.2% *vs.* 17.8%, *p*=0.09), or both types (33.3% *vs.* 22.2%, *p*=0.15).

Grade 1-2 irAEs were more frequent in patients who received at least one dose of Sinovac compared to those who did not (23.7% *vs.* 8.9%, *p*=0.04), whereas no significant differences were observed for mRNA-based vaccination (18.6% *vs.* 19.4%, *p*=0.91) or both types (26.3% *vs.* 13.6%, *p*=0.06). Grade 3-4 irAEs were comparable across all vaccination groups and stratifications (all *p*>0.05).

Grade 1-2 irAEs were predominantly dermatological and endocrine across all vaccination groups. In the Sinovac group, dermatological (8.6%), pulmonary (2.9%), and endocrine (5.7%) events were observed. In the mRNA-based group, dermatological (6.7%) and endocrine (2.2%) toxicities were reported. In patients who received both vaccine types, dermatological (10.5%), pulmonary (7.0%), endocrine (5.3%), and hematological (1.8%) toxicities were recorded (Figure 5).

Grade 3-4 irAEs were uncommon and showed no clear predominance among vaccination groups. In the Sinovac group, severe dermatological (2.8%), pulmonary (5.6%), and cardiac (5.6%) toxicities were observed. In the mRNA-based group, severe pulmonary toxicity occurred in 8.9% of patients. Among patients who received both vaccine types, grade 3-4 pulmonary (1.8%), endocrine (1.8%),

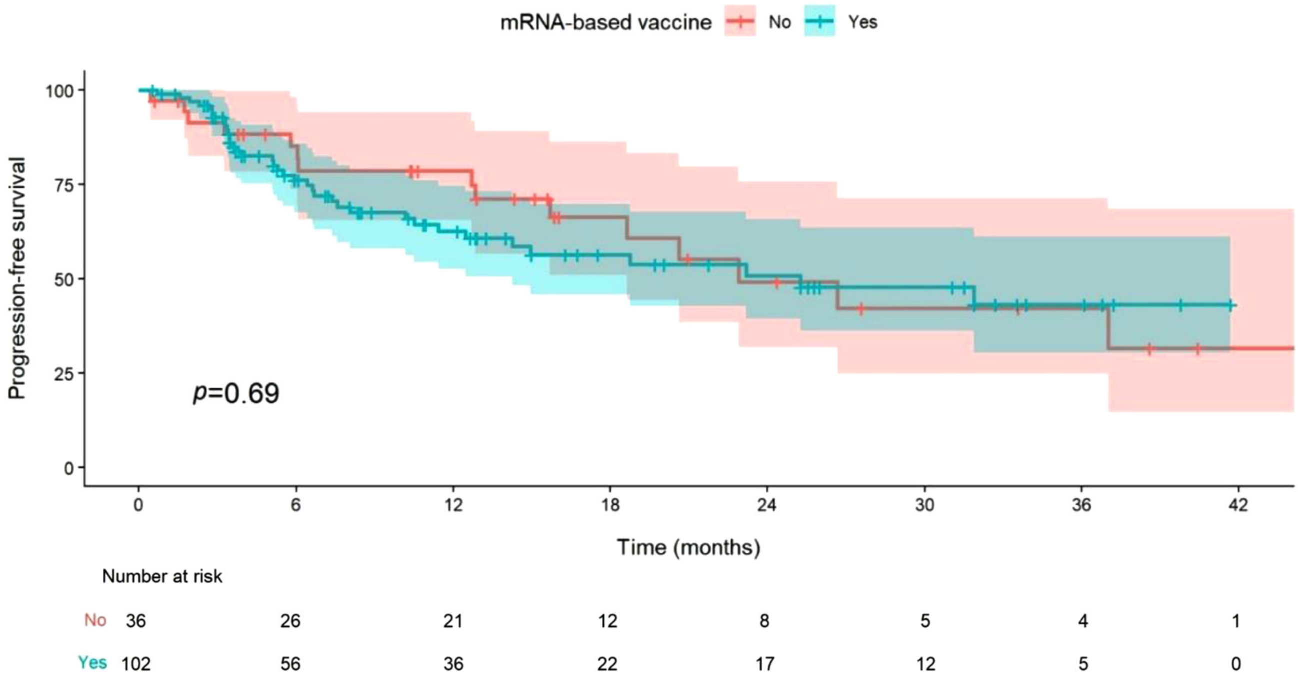

Figure 2. *Progression-free survival according to receipt of at least one dose of an mRNA COVID-19 vaccine.*

and gastrointestinal (7.0%) toxicities were reported (Figure 6).

In multivariate Cox regression analysis adjusting for age, Eastern Cooperative Oncology Group performance score (ECOG PS), and expression of programmed cell death 1 protein ligand 1 (PD-L1) , COVID-19 vaccination type was not independently associated with PFS (global p=0.44). Compared with the virion-based group, neither the mRNA-based group [hazard ratio (HR)=1.05, 95% confidence interval (CI=)=0.51-2.18; p=0.89] nor the both- types group (HR=1.50, 95% CI=0.76-2.96; p=0.24) showed a significant difference in PFS. Age (HR=1.52, 95% CI=0.86-2.68; p=0.15), ECOG PS (HR=1.06, 95% CI=0.59-1.92; p=0.85), and PD-L1 category (global p=0.19) were also not independently associated with PFS.

Discussion

In this multicenter retrospective study, we found that COVID-19 vaccination type did not significantly influence the efficacy or safety of nivolumab in patients with driver mutation-negative metastatic NSCLC. ORR, CBR, and PFS were comparable among patients who received virion-based (Sinovac) vaccine only, mRNA-based vaccine only, or both vaccine types. Likewise, the incidence of any-grade and grade 3-4 irAEs did not differ significantly across vaccination groups, although grade 1-2 irAEs were more frequent among patients who had received at least one dose of a virion-based vaccine. Importantly, the primary aim of this study was to evaluate whether the long-term efficacy and safety outcomes of second-line nivolumab differ according to the type of prior COVID-19 vaccination (virion-based *vs.* mRNA-based). In this context, the main clinically relevant finding is the absence of any meaningful difference between the two vaccine platforms in terms of response to nivolumab, survival, and immune-related toxicity.

We specifically focused on patients with metastatic NSCLC receiving second-line nivolumab because PD1 blockade represents a well-established standard of care in this setting and is highly dependent on intact host

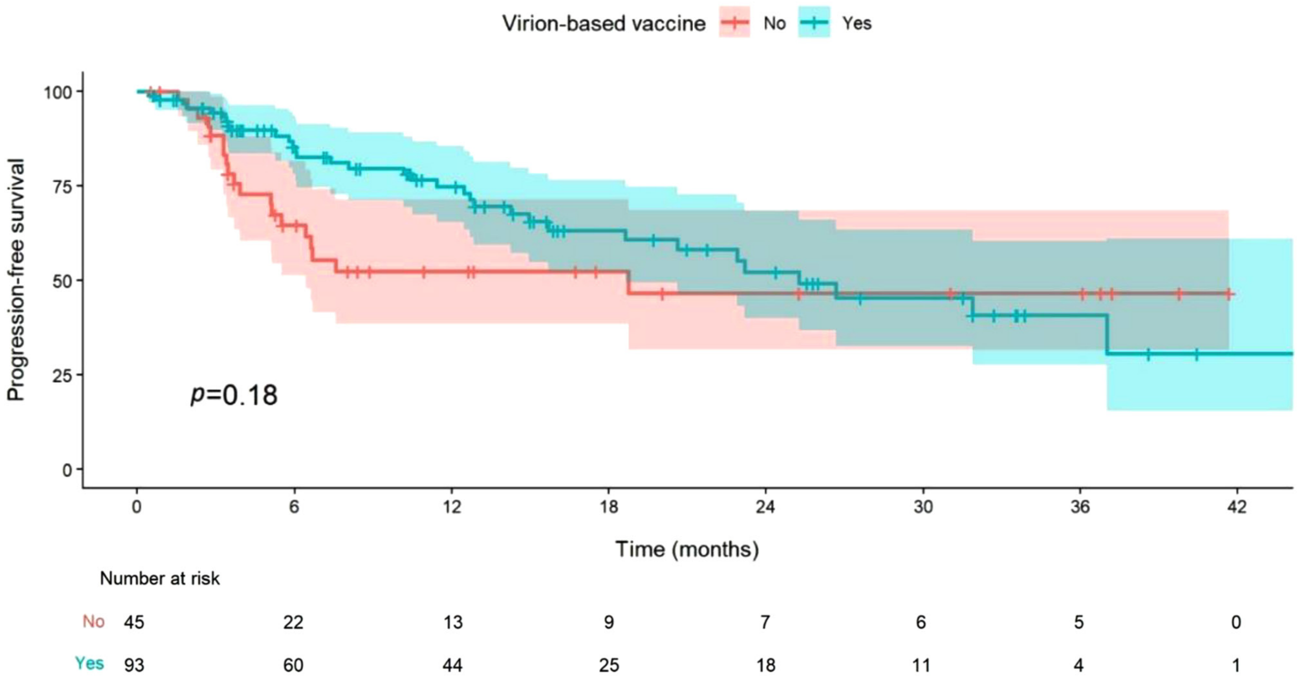

Figure 3. *Progression-free survival according to receipt of at least one dose of a virion-based (Sinovac) COVID-19 vaccine.*

antitumor immunity (7). ICIs enhance T-cell-mediated immune responses, but their activity can be influenced by external immune-modulating factors, including infections and vaccinations. In this context, both suppression and exaggeration of immune responses are clinically relevant: excessive immune activation may increase the risk of irAEs, whereas immune suppression or immune deviation could theoretically impair antitumor efficacy (12, 13). Such alterations in immune homeostasis are particularly important in patients treated with nivolumab, as both treatment response and toxicity profiles have been shown to correlate with survival outcomes and quality of life [reviewed in (14)]. Therefore, understanding whether COVID-19 vaccines modulate long-term immune responses in a way that affects nivolumab efficacy or safety remains clinically relevant.

Both mRNA-based and virion-based COVID-19 vaccines have demonstrated high effectiveness in preventing severe COVID-19, hospitalization, and death among patients with cancer, with generally manageable and acceptable safety profiles [reviewed in (15, 16)]. In real-world oncology cohorts, vaccination has not been associated with excess severe toxicity, even among patients receiving ICIs (5). Despite emerging evidence suggesting that mRNA-based COVID-19 vaccines may enhance the efficacy of ICIs (17), we observed no significant difference in nivolumab response between patients who received virion-based vaccines and those who received mRNA-based vaccines. Notably, prior reports exploring vaccine-ICI interactions have largely focused on vaccinations administered shortly before or after ICI initiation (9, 18, 19), often within 100 days of treatment start, whereas our study specifically addressed the potential long-term impact of COVID-19 vaccination by including only patients who initiated nivolumab at least 6 months after their last vaccine dose.

The median PFS observed in our cohort was substantially longer than that reported in the pivotal second-line nivolumab trials and large real-world series. In the CheckMate 017 (7) and 057 (20) trials, median PFS with

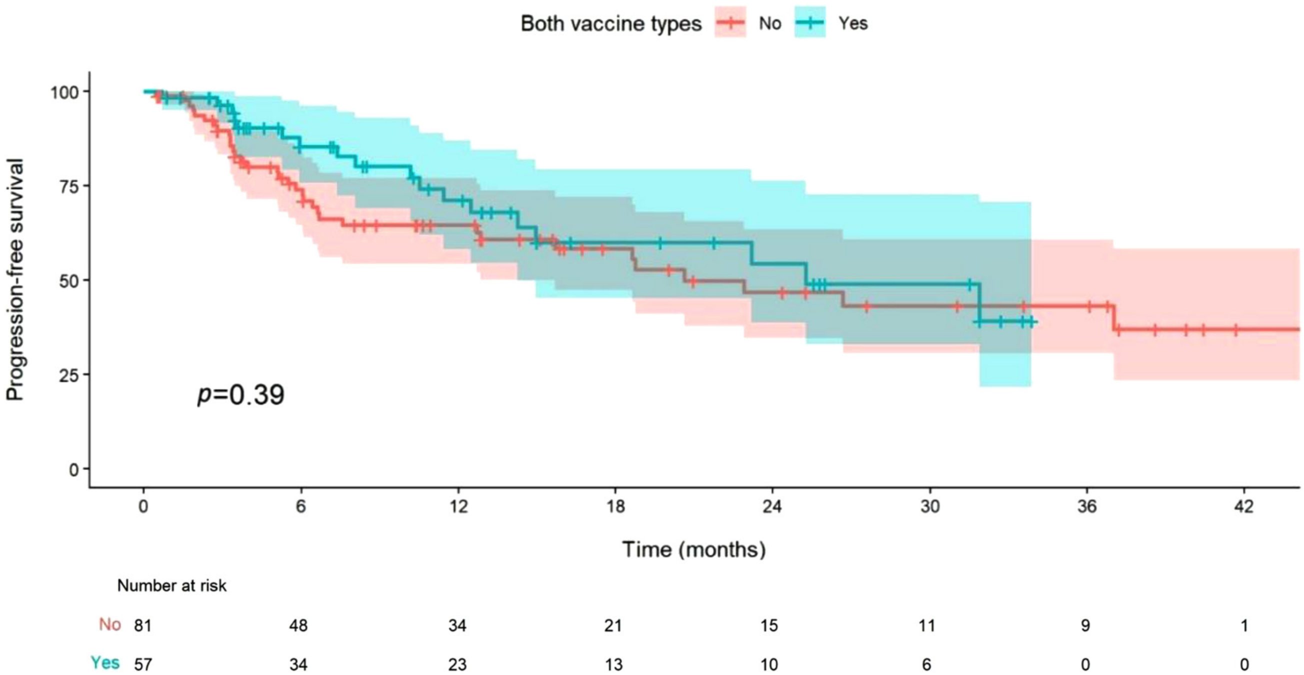

Figure 4. *Progression-free survival according to receipt of both COVID-19 vaccine types.*

nivolumab was 3.5 months in patients with squamous NSCLC and 2.3 months in those with non-squamous NSCLC, with ORR of approximately 19-20% and CBR of 45-50%. In contrast, median PFS in our study exceeded 20 months across vaccination groups. In addition, both the ORR and CBR observed in our cohort were markedly higher than those reported in historical nivolumab-treated population (21, 22). However, it should be emphasized that the unexpectedly prolonged PFS was not the primary focus of our study. Our main objective was to assess whether virion-based and mRNA-based vaccines differ in their impact on nivolumab efficacy and safety, and our key finding is the consistent similarity of outcomes across both vaccine platforms.

The most plausible explanation for the unexpectedly high PFS, ORR, and CBR observed in our study is related to selection and information bias inherent to our dataset. A substantial proportion of patients (81.9%) were still alive at the time of analysis, and it was predominantly possible to retrieve vaccination data for these surviving patients, whereas such data were frequently unavailable for patients who had died, leading to their underrepresentation. Consequently, patients with poorer outcomes (*i.e.*, early progression or death) were less likely to be included, thereby reducing the number of observed PFS events. In addition, many patients had not yet experienced progression at the time of analysis due to ongoing follow-up, further limiting event capture. The Kaplan-Meier curves also showed some degree of crossing between groups, which may suggest a potential violation of the proportional hazards assumption and indicates that relative treatment effects may vary over time. However, given the limited number of events and the retrospective design, this pattern is more likely attributable to small sample size and censoring rather than a true time-dependent effect. Taken together, these factors likely resulted in an artificial prolongation of the estimated median PFS, reflecting survivor and censoring bias rather than a true biological effect, and should therefore be interpreted cautiously.

In addition to this methodological explanation, a secondary and more speculative hypothesis is that prior

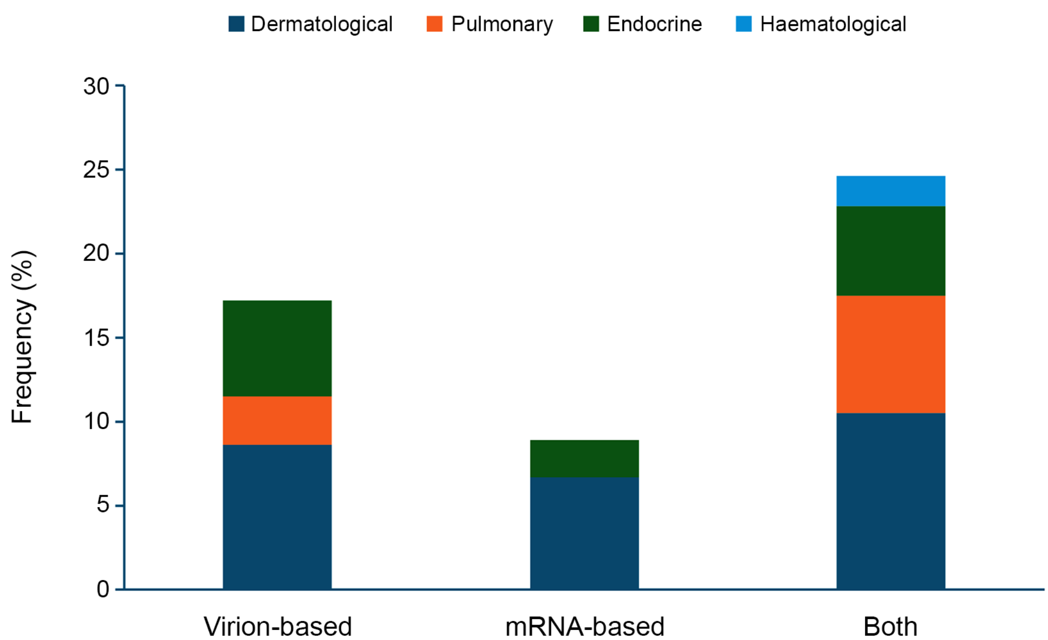

Figure 5. *Distribution of grade 1-2 immune-related adverse events according to COVID-19 vaccine type.*

COVID-19 vaccination may have modestly contributed to improved antitumor immunity and prolonged PFS. Importantly, all patients in our cohort were vaccinated, whereas historical nivolumab trials were conducted in entirely unvaccinated populations. Emerging experimental evidence suggests that SARS-CoV-2 vaccination may enhance sensitivity to immune checkpoint blockade (23, 24). In a landmark preclinical study, mRNA-based SARS-CoV-2 vaccination reshaped the tumor immune microenvironment and rendered immunologically 'cold' tumors responsive to PD1 blockade (9).

Clinical data on this issue remain limited and heterogeneous. In the INVIDIa-2 study, patients with cancer receiving ICIs who had been vaccinated against influenza demonstrated significantly improved OS and PFS compared with unvaccinated patients (25). In contrast, a meta-analysis reported similar mortality rates between influenza-vaccinated and unvaccinated patients treated with ICIs (26). Taken together, while vaccine-induced immune modulation represents a biologically plausible hypothesis, our data strongly suggest that the unusually prolonged PFS in our cohort is primarily driven by survivor bias and immature follow-up rather than a definitive vaccine-related effect. The potential contribution of prior vaccination should therefore be considered hypothesis-generating.

We acknowledge that favorable baseline characteristics, including ECOG PS of 0-1 in all patients and a high prevalence of PD-L1 expression ≥1%, likely contributed to improved outcomes. Moreover, heterogeneity in prior disease stage and first-line treatment may have selected for patients with more indolent disease biology. However, these factors alone are unlikely to fully account for a median PFS exceeding 20 months in a second-line nivolumab population. Therefore, while selection and survivor bias cannot be excluded, the consistent deviation from historical PFS benchmarks should be interpreted cautiously and primarily attributed to methodological factors.

With respect to subgroup analyses, a substantial proportion of patients with PD-L1 expression ≥50% had received both vaccine types, and in this subgroup, median PFS was numerically longer, although the difference did

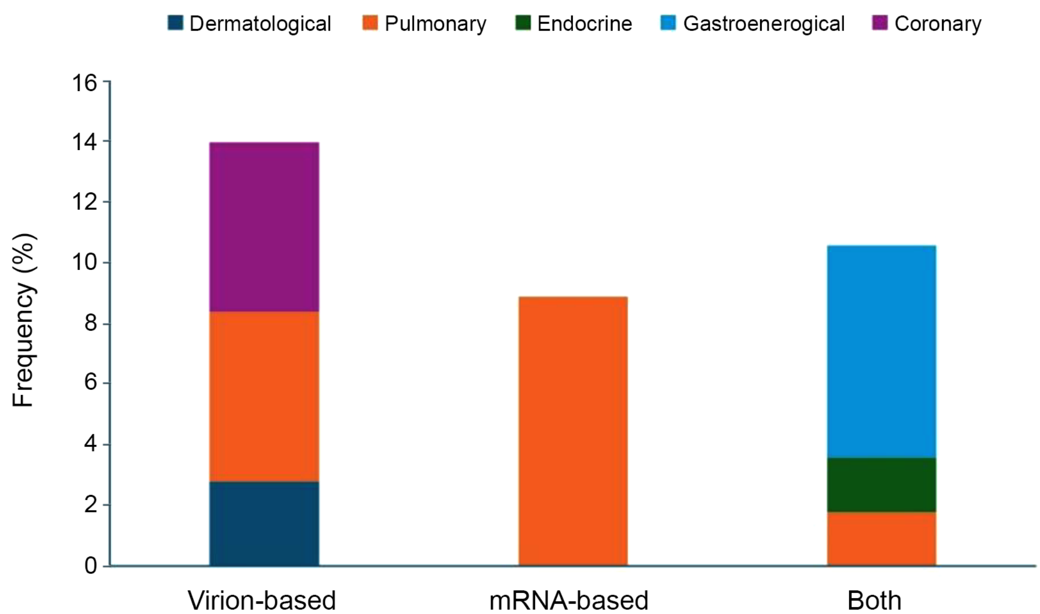

Figure 6. *Distribution of grade 3-4 immune-related adverse events according to COVID-19 vaccine type.*

not reach statistical significance. Importantly, no difference in irAEs was observed in this high PD-L1-expressing population, suggesting that dual-platform vaccination does not adversely affect the safety profile of nivolumab.

With respect to safety, COVID-19 vaccination type was not associated with an increased risk of severe irAEs in our cohort. The incidence of any-grade and grade 3-4 irAEs was comparable across vaccination groups, and the only significant difference observed was a higher frequency of grade 1-2 irAEs among patients who had received a virion-based vaccine. Data specifically addressing irAEs according to virion-based vaccination in patients receiving ICIs remain extremely limited. One real-world analysis of inactivated SARS-CoV-2 vaccines in patients with cancer, including a subgroup receiving PD1 blockade, did not demonstrate a significant increase in immune-related toxicity, although detailed platform-specific comparisons were not performed (27). This discrepancy may be attributable to differences in sample size, patient characteristics, ethnic composition, study design, and variations in the timing of vaccination relative to ICI initiation.

Importantly, no signal of excess severe toxicity was detected in patients vaccinated with mRNA-based vaccines, and these findings are consistent with prior real-world studies demonstrating that COVID-19 vaccination is generally safe in patients receiving ICIs (18, 28-30). Overall, our data provide additional reassurance that neither mRNA-based nor virion-based COVID-19 vaccines exacerbate immune-mediated toxicity in patients treated with nivolumab, and that the modest increase in low-grade irAEs observed with virion-based vaccination is unlikely to be clinically consequential.

Study limitations and strengths. Several limitations of our study should be acknowledged. Firstly, the retrospective design introduced the potential for selection bias and unmeasured confounding, and causal inferences cannot be definitively established. Secondly, although this is one of the largest cohorts to date evaluating COVID-19 vaccination in patients receiving ICIs, the sample size, particularly within the virion-based subgroup may have limited the power to detect small differences in efficacy or rare irAEs. Thirdly, vaccine allocation was not randomized, and residual confounding related to patient characteristics or healthcare access cannot be fully excluded.

An important limitation is the absence of an unvaccinated control group, which precluded a direct comparison between vaccinated and unvaccinated patients and limited our ability to formally assess the independent effect of COVID-19 vaccination on clinical outcomes. Consequently, we were unable to perform analyses stratified by vaccination status (vaccinated *vs.* unvaccinated). The requirement that patients had started nivolumab therapy at least 6 months after COVID-19 vaccination may have introduced selection and survivor bias, as only patients who remained alive and progression-free long enough after vaccination were included. While this may have partly contributed to the prolonged PFS observed in our cohort, it also reflects the deliberate design of our study to focus on the long-term immunologic impact of vaccination rather than short-term vaccine-ICI interactions.

In addition, follow-up remains relatively immature, and the median overall survival point has not yet been reached, precluding a mature overall survival analysis at the time of this report. Moreover, data on potentially relevant biological variables such as tumor mutational burden, human-like antigen (HLA) genotype, microbiome composition, and post-vaccination immune profiling were not available, precluding mechanistic validation of the hypothesis that COVID-19 vaccination may have contributed to prolonged PFS.

Despite these limitations, our study has several important strengths. By including only patients treated with second-line nivolumab, we minimized treatment-line heterogeneity and enhanced internal consistency. The multicenter real-world design improves generalizability, while the head-to-head comparison of virion-based and mRNA-based vaccines and the long post-vaccination interval strengthen the relevance of our findings. The comprehensive assessment of both efficacy and safety endpoints, together with multivariable adjustment for key clinical covariates, supports the robustness of our conclusions.

From a clinical perspective, the central message of our study is not the absolute magnitude of PFS, but rather that the efficacy and safety of second-line nivolumab are comparable regardless of the type of prior COVID-19 vaccination (virion-based *vs*. mRNA-based).

Conclusion

In this multicenter real-world cohort, virion-based and mRNA-based COVID-19 vaccines showed comparable long-term efficacy and safety in patients with metastatic NSCLC receiving second-line nivolumab. No clinically meaningful differences were observed in response rates, PFS, or immune-related toxicity between the two vaccine platforms, providing reassuring evidence that the choice of COVID-19 vaccine does not adversely affect treatment outcomes during PD1 blockade.

Conflicts of Interest

The Authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contributions

B.K.: Writing - original draft. B.K, E.K.K.: Conceptualization. M.B, and C.K: Supervision. Y.E. and Ö.A.Y: Statistical analysis. S.Y. and N.K.: Methodology. G.G.G. and G.A.: Investigation. F.K.U. and A.A.: Data collection. S.E.D. and Z.U.: Editing. O.S.: Review. All Authors approved the final manuscript.

Acknowledgements

The Authors declare that there are no acknowledgements.

Funding

This study did not receive any financial support or funding.

Artificial Intelligence (AI) Disclosure

Artificial intelligence tools were used only for language editing and grammar correction. No AI tools were used in the study design, data analysis, or interpretation of the results.

References

1 Gurney JK, Millar E, Dunn A, Pirie R, Mako M, Manderson J, Hardie C, Jackson CGCA, North R, Ruka M, Scott N, Sarfati D: The impact of the COVID-19 pandemic on cancer diagnosis and service access in New Zealand-a country pursuing COVID-19 elimination. Lancet Reg Health West Pac 10: 100127, 2021. DOI: 10.1016/j.lanwpc.2021.100127

2 Trifanescu OG, Gales L, Bacinschi X, Serbanescu L, Georgescu M, Sandu A, Michire A, Anghel R: Impact of the COVID-19 pandemic on treatment and oncologic outcomes for cancer patients in Romania. In Vivo 36(2): 934-941, 2022. DOI: 10.21873/invivo.12783

3 Lee HE, Jeong NY, Park M, Lim E, Kim JA, Won H, Kim CJ, Park SM, Choi NK: Effectiveness of COVID-19 vaccines against severe outcomes in cancer patients: Real-world evidence from self-controlled risk interval and retrospective cohort studies. J Infect Public Health 17(5): 854-861, 2024. DOI: 10.1016/j.jiph.2024.03.015

4 Lazar Neto F, Mercadé-Besora N, Raventós B, Pérez-Crespo L, Castro Junior G, Ranzani OT, Duarte-Salles T: Effectiveness of COVID-19 vaccines against severe COVID-19 among patients with cancer in Catalonia, Spain. Nat Commun 15(1): 5088, 2024. DOI: 10.1038/s41467-024-49285-y

5 Widman AJ, Cohen B, Park V, McClure T, Wolchok J, Kamboj M: Immune-related adverse events among COVID-19-vaccinated patients with cancer receiving immune checkpoint blockade. J Natl Compr Canc Netw 20(10): 1134-1138, 2022. DOI: 10.6004/jnccn.2022.7048

6 Ruiz JI, Lopez-Olivo MA, Geng Y, Suarez-Almazor ME: COVID-19 vaccination in patients with cancer receiving immune checkpoint inhibitors: a systematic review and meta-analysis. J Immunother Cancer 11(2): e006246, 2023. DOI: 10.1136/jitc-2022-006246

7 Brahmer J, Reckamp KL, Baas P, Crinò L, Eberhardt WE, Poddubskaya E, Antonia S, Pluzanski A, Vokes EE, Holgado E, Waterhouse D, Ready N, Gainor J, Arén Frontera O, Havel L, Steins M, Garassino MC, Aerts JG, Domine M, Paz-Ares L, Reck M, Baudelet C, Harbison CT, Lestini B, Spigel DR: Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. N Engl J Med 373(2): 123-135, 2015. DOI: 10.1056/NEJMoa1504627

8 Maimon O, Nisman B, Broier S, Ben-David I, Kuznetz A, Gelfand Y, Mizrahi A, Prus E, Fuchs I, Lotem M, Popovtzer A, Khutsurauli S, Meirovitz A, Nechushtan H, Peretz T: The active tumor vaccination in combination with CDK4/6 inhibitor treatment: a case report. Anticancer Res 44(8): 3543-3550, 2024. DOI: 10.21873/anticanres.17175

9 Grippin AJ, Marconi C, Copling S, Li N, Braun C, Woody C, Young E, Gupta P, Wang M, Wu A, Jeong SD, Soni D, Weidert F, Xie C, Goldenberg E, Kim A, Zhao C, DeVries A, Castillo P, Lohray R, Rooney MK, Schrank BR, Wang Y, Ma Y, Chang E, Kouzy R, Dyson K, Jafarnia J, Nariman N, Gladish G, New J, Argueta A, Amaya D, Thomas N, Doty A, Chen J, Copling N, Alatrash G, Simon J, Davies AB, Dennis W, Liang R, Lewis J, Wei X, Rinsurongkawong W, Vaporciyan AA, Johns A, D3CODE Team, Lee J, Lee JH, Sun R, Sharma P, Tran H, Zhang J, Gibbons DL, Wargo J, Kim BYS, Heymach JV, Mendez-Gomez HR, Jiang W, Sayour EJ, Lin SH: SARS-CoV-2 mRNA vaccines sensitize tumours to immune checkpoint blockade. Nature 647(8089): 488-497, 2025. DOI: 10.1038/s41586-025-09655-y

10 Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J: New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 45(2): 228-247, 2009. DOI: 10.1016/j.ejca.2008.10.026

11 Freites-Martinez A, Santana N, Arias-Santiago S, Viera A: Using the Common Terminology Criteria for Adverse Events (CTCAE - Version 5.0) to evaluate the severity of adverse events of anticancer therapies. Actas Dermosifiliogr 112(1): 90-92, 2021. DOI: 10.1016/j.ad.2019.05.009

12 Brest P, Mograbi B, Hofman P, Milano G: COVID-19 vaccination and cancer immunotherapy: should they stick together? Br J Cancer 126(1): 1-3, 2022. DOI: 10.1038/s41416-021-01618-0

13 Postow MA, Sidlow R, Hellmann MD: Immune-related adverse events associated with immune checkpoint blockade. N Engl J Med 378(2): 158-168, 2018. DOI: 10.1056/NEJMra1703481

14 Rathod M, Kadari M, Kadavath AD, Thomas C, Raveendran A, Jagtap M, Undela K: Safety of immune checkpoint inhibitors: A systematic review of disproportionality analysis studies. Eur J Clin Pharmacol 82(2): 35, 2026. DOI: 10.1007/s00228-025-03960-1

15 Korang SK, von Rohden E, Veroniki AA, Ong G, Ngalamika O, Siddiqui F, Juul S, Nielsen EE, Feinberg JB, Petersen JJ, Legart C, Kokogho A, Maagaard M, Klingenberg S, Thabane L, Bardach A, Ciapponi A, Thomsen AR, Jakobsen JC, Gluud C: Vaccines to prevent COVID-19: A living systematic review with Trial Sequential Analysis and network meta-analysis of randomized clinical trials. PLoS One 17(1): e0260733, 2022. DOI: 10.1371/journal.pone.0260733

16 Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, Diemert D, Spector SA, Rouphael N, Creech CB, McGettigan J, Khetan S, Segall N, Solis J, Brosz A, Fierro C, Schwartz H, Neuzil K, Corey L, Gilbert P, Janes H, Follmann D, Marovich M, Mascola J, Polakowski L, Ledgerwood J, Graham BS, Bennett H, Pajon R, Knightly C, Leav B, Deng W, Zhou H, Han S, Ivarsson M, Miller J, Zaks T, COVE Study Group: Efficacy and safety of the mRNA-

1273 SARS-CoV-2 vaccine. N Engl J Med 384(5): 403-416, 2021. DOI: 10.1056/NEJMoa2035389
17 Wang CC, Wang CC, Yang CC, Hwang TZ, Lien CF, Shih YC, Yeh SA, Hsieh MC: Response to letter to the editor: Fully COVID -19 vaccinated status enhanced the efficacy of immune checkpoint inhibitors in patients with recurrent or metastatic head and neck squamous cell carcinoma. Head Neck 48(4): 1143-1144, 2026. DOI: 10.1002/hed.70173
18 Waissengrin B, Agbarya A, Safadi E, Padova H, Wolf I: Short-term safety of the BNT162b2 mRNA COVID-19 vaccine in patients with cancer treated with immune checkpoint inhibitors. Lancet Oncol 22(5): 581-583, 2021. DOI: 10.1016/s1470-2045(21)00155-8
19 Switzer B, Haanen J, Lorigan PC, Puzanov I, Turajlic S: Clinical and immunologic implications of COVID-19 in patients with melanoma and renal cell carcinoma receiving immune checkpoint inhibitors. J Immunother Cancer 9(7): e002835, 2021. DOI: 10.1136/jitc-2021-002835
20 Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, Chow LQ, Vokes EE, Felip E, Holgado E, Barlesi F, Kohlhäufl M, Arrieta O, Burgio MA, Fayette J, Lena H, Poddubskaya E, Gerber DE, Gettinger SN, Rudin CM, Rizvi N, Crinò L, Blumenschein GR Jr, Antonia SJ, Dorange C, Harbison CT, Graf Finckenstein F, Brahmer JR: Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. N Engl J Med 373(17): 1627-1639, 2015. DOI: 10.1056/NEJMoa1507643
21 Lim SM, Kim SW, Cho BC, Kang JH, Ahn MJ, Kim DW, Kim YC, Lee JS, Lee JS, Lee SY, Park KU, An HJ, Cho EK, Jang TW, Kim BS, Kim JH, Lee SS, Na II, Yoo SS, Lee KH: Real-world experience of nivolumab in non-small cell lung cancer in Korea. Cancer Res Treat 52(4): 1112-1119, 2020. DOI: 10.4143/crt.2020.245
22 Morita R, Okishio K, Shimizu J, Saito H, Sakai H, Kim YH, Hataji O, Yomota M, Nishio M, Aoe K, Kanai O, Kumagai T, Kibata K, Tsukamoto H, Oizumi S, Fujimoto D, Tanaka H, Mizuno K, Masuda T, Kozuki T, Haku T, Suzuki H, Okamoto I, Hoshiyama H, Ueda J, Ohe Y: Real-world effectiveness and safety of nivolumab in patients with non-small cell lung cancer: A multicenter retrospective observational study in Japan. Lung Cancer 140: 8-18, 2020. DOI: 10.1016/j.lungcan.2019.11.014
23 Qian Y, Zhu Z, Mo YY, Zhang Z: COVID-19 vaccination is associated with enhanced efficacy of anti-PD-(L)1 immunotherapy in advanced NSCLC patients: a real-world study. Infect Agent Cancer 18(1): 50, 2023. DOI: 10.1186/s13027-023-00526-7
24 Arbel R, Rokach L, Razi T, Tadmor T: Validation of "SARS-CoV-2 mRNA vaccines sensitize tumors to immune checkpoint blockade" in an independent cohort of 4,407 patients. Cancer Lett 643: 218319, 2026. DOI: 10.1016/j.canlet.2026.218319
25 Bersanelli M, Verzoni E, Cortellini A, Giusti R, Calvetti L, Ermacora P, Di Napoli M, Catino A, Guadalupi V, Guaitoli G, Scotti V, Mazzoni F, Veccia A, Guglielmini PF, Perrone F, Maruzzo M, Rossi E, Casadei C, Montesarchio V, Grossi F, Rizzo M, Travagliato Liboria MG, Mencoboni M, Zustovich F, Fratino L, Accettura C, Cinieri S, Camerini A, Sorarù M, Zucali PA, Ricciardi S, Russo A, Negrini G, Banzi MC, Lacidogna G, Fornarini G, Laera L, Mucciarini C, Santoni M, Mosillo C, Bonetti A, Longo L, Sartori D, Baldini E, Guida M, Iannopollo M, Bordonaro R, Morelli MF, Tagliaferri P, Spada M, Ceribelli A, Silva RR, Nolè F, Beretta G, Giovanis P, Santini D, Luzi Fedeli S, Nanni O, Maiello E, Labianca R, Pinto C, Clemente A, Tognetto M, De Giorgi U, Pignata S, Di Maio M, Buti S, Giannarelli D, FICOG group (Federation of Italian Cooperative Oncology Groups): Impact of influenza vaccination on survival of patients with advanced cancer receiving immune checkpoint inhibitors (INVIDIa-2): final results of the multicentre, prospective, observational study. EClinicalMedicine 61: 102044, 2023. DOI: 10.1016/j.eclinm.2023.102044
26 Tsiakos K, Kyriakoulis KG, Kollias A, Kyriakoulis IG, Poulakou G, Syrigos K: Influenza vaccination in cancer patients treated with immune checkpoint inhibitors: a systematic review and meta-analysis. J Immunother 45(6): 291-298, 2022. DOI: 10.1097/cji.0000000000000424
27 Ma Y, Liu N, Wang Y, Zeng J, Hu YY, Hao W, Shi H, Zhu P, Lv J, Fan W, Wang X: Immune checkpoint blocking impact and nomogram prediction of COVID-19 inactivated vaccine seroconversion in patients with cancer: a propensity-score matched analysis. J Immunother Cancer 9(11): e003712, 2021. DOI: 10.1136/jitc-2021-003712
28 Chen YW, Tucker MD, Beckermann KE, Iams WT, Rini BI, Johnson DB: COVID-19 mRNA vaccines and immune-related adverse events in cancer patients treated with immune checkpoint inhibitors. Eur J Cancer 155: 291-293, 2021. DOI: 10.1016/j.ejca.2021.07.017
29 Dimitrov G, Argirova R, Valkov T: Impact of COVID-19 and vaccination on long-term survival in patients with solid malignancies: A nationwide cohort study. Eur J Cancer 239: 116708, 2026. DOI: 10.1016/j.ejca.2026.116708
30 Sundaram ME: Vaccine safety for individuals receiving immune checkpoint inhibitor therapy: A narrative review of current literature and recommendations for future research. Hum Vaccin Immunother 22(1): 2607893, 2026. DOI: 10.1080/21645515.2025.2607893