Cancer Immunology, Immunotherapy (2023) 72:3217–3228
https://doi.org/10.1007/s00262-023-03489-1

RESEARCH

Immune-related adverse events and disease outcomes after the third dose of SARS-CoV-2 mRNA-BNT162b2 vaccine in cancer patients receiving immune checkpoint inhibitors

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Received: 12 June 2022 / Accepted: 27 June 2023 / Published online: 10 July 2023

Abstract

Background The clinical implications of the third dose of coronavirus disease 2019 (COVID-19) vaccines in patients receiving immune checkpoint inhibitors are currently unknown. We performed a prospective analysis of the Vax-On-Third study to investigate the effects of antibody response on immune-related adverse events (irAEs) and disease outcomes.

Methods Recipients of the booster dose of SARS-CoV-2 mRNA-BNT162b2 vaccine who had received at least one course of an anti-PD-1/PD-L1 treatment before vaccination for an advanced solid malignancy were eligible.

Results The current analysis included 56 patients with metastatic disease (median age: 66 years; male: 71%), most of whom had a lung cancer diagnosis and were being treated with pembrolizumab- or nivolumab-based regimens. The optimal cut-point antibody titer of 486 BAU/mL allowed a dichotomization of recipients into low-responders (Low-R, < 486 BAU/mL) or high-responders (High-R, ≥ 486 BAU/mL). After a median follow-up time of 226 days, 21.4% of patients experienced moderate to severe irAEs without any recrudescence of immune toxicities preceding the booster dose. The frequencies of irAE before and after the third dose did not differ, but an increase in the cumulative incidence of immuno-related thyroiditis was observed within the High-R subgroup. On multivariate analysis, an enhanced humoral response correlated with a better outcome in terms of durable clinical benefit, which resulted in a significant reduction in the risk of disease control loss but not mortality.

Conclusions Our findings would strengthen the recommendation not to change anti-PD-1/PD-L1 treatment plans based on current or future immunization schedules, implying that all these patients should be closely monitored.

Keywords COVID-19 vaccination · Antibody response · Cancer patients · Immune-checkpoint inhibitors · Immune-related adverse events · Disease outcomes

Introduction

The global increase in SARS-CoV-2 variants of concern (VOC) breakthrough infections among fully vaccinated cancer patients has prompted the need for additional interventions, including supplemental vaccine dosing [1, 2]. A third dose of mRNA-BNT162b2 vaccine (tozinameran) is able to elicit a stronger antibody response than the initial two-dose series in most patients with solid malignancies receiving active treatments [3]. A viable recall of T cell-mediated response is thought to underlie the enhancement of humoral immunogenicity [4]. While the intensification of adaptive immunity induced by booster dosing would confer protection against symptomatic COVID-19 even

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in recipients with no or waning response [5–8], it renews concerns about clinical interactions with immune checkpoint inhibitors (ICIs) in terms of safety and efficacy [9]. The evidence of an unincreased risk of immune-related adverse events (irAEs) following immunization supports the short-term safety of COVID-19 vaccines in patients with cancer receiving ICIs [10]. However, the effects of booster dosing on new or worsening pre-existing irAEs and their potential interactions with the magnitude of the immune response have not been thoroughly elucidated [11]. In general, any vaccination can induce increased cytokine release, which is responsible for systemic symptoms in some recipients. This reaction could theoretically trigger new immune responses or enhance an ongoing inflammatory process. Specifically, COVID-19 mRNA-based vaccines encode a SARS-CoV-2 transmembrane spike protein, whose shedding and binding to angiotensin-converting enzyme 2 (ACE2) in human tissues may exert proinflammatory effects [12]. On the other hand, immune checkpoint therapies that block the co-inhibitory pathway of programmed cell death protein-1 (PD-1) and its cognate ligand-1 (PD-L1) induce reactivation of exhausted T cells. It is conceivable that an enhanced adaptive response against tumor antigens may also involve the reactivation of SARS-CoV-2 spike protein-specific T cells, leading to increased cytokine release and subsequent clinical events [13]. The issue of whether the enhanced effects of the booster dose have a functional impact on the activity of ICI treatment arises and remains further unaddressed [14]. We therefore performed a pre-planned subgroup analysis of the Vax-On-Third study to investigate whether the third dose of tozinameran affects the clinical outcomes of patients with advanced solid malignancies receiving monoclonal antibodies targeting the PD-1/PD-L1 axis.

Materials and methods

Study design and participants

The Vax-On-Third was a prospective, observational, cohort study, whose design and primary results were previously reported (clinical study identifier: EudraCT number 2021-002611-54) [15]. The study protocol follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) standards. The referring Ethics Committee approved the study, and all patients provided written informed consent (protocol number: 1407/CE Lazio1). Participants who were eligible for the current analysis met the following inclusion criteria: histologically confirmed diagnosis of solid malignancy, locally advanced or metastatic extent of disease, at least one dose of an anti-PD-1 (nivolumab, pembrolizumab, or cemiplimab) or anti-PD-L1 (atezolizumab, durvalumab, or avelumab) agent received before the third dose of tozinameran, no evidence of progressive disease (PD) on restaging performed within 8 weeks before the third dose, subsequent disease reassessment carried out within 6 months of the third dose, and availability of IgG antibody titer against receptor binding domain of SARS-CoV-2 Spike protein (RBD-S1) tested 4 weeks after the third dose. The SARS-CoV-2 IgG II Quant assay on the ARCHITECT i2000sr automated platform (Abbott Laboratories, Diagnostics Division, Sligo, Ireland) was used to detect anti-RBD-S1 IgG antibodies according to the manufacturer's instructions [16]. The results were provided as arbitrary units per milliliter (AU/mL) within a linear range that expanded to 80,000 with an automated dilution. The serological titers obtained were converted from AU to binding antibody units (BAU) after WHO International Standards for anti-SARS-CoV-2 immunoglobulin testing were released (1 Abbott AU corresponds to 0.142 WHO BAU) [17]. The primary end points were safety and disease outcomes based on anti-RDB-S1 IgG titer levels. The National Cancer Institute's Common Terminology Criteria for Adverse Events, version 5.0, were used to classify treatment-related toxicities. We reviewed all patient imaging to determine response rates as per Response Evaluation Criteria in Solid Tumors (RECIST 1.1) [18]. In addition to objective responses defined by RECIST, we also decided to aggregate patients with complete (CR) or partial (PR) responses to those showing a stable disease (SD) lasting more than 6 months. This group (DCB, durable clinical benefit) was therefore compared to those who did not demonstrate a durable clinical benefit (NCB group, PD or SD lasting less than 6 months). The outcomes of survival were investigated in terms of vaccine-related time-to-treatment failure (V-TTF, which referred to the time elapsed from the treatment with an anti-PD-1/PD-L1 agent immediately preceding the booster dose to its permanent discontinuation for any reason) and overall survival (OS, which referred to the time elapsed from initiation of an anti-PD-1/PD-L1 treatment to death for any reason). Patients who did not progress or die as of the last interim analysis were censored (April 30, 2023).

Statistical analysis

A mean with standard deviation was used to describe normally distributed variables, while a median with a 95% confidence interval (CI) or interquartile range (IQR) was reported for skewed variables. Comparative assessments were performed by applying Pearson's χ^2 test for categorical data and Mann–Whitney *U* test for continuous variables. The Wilcoxon signed-rank and McNemar tests were used for pairwise comparisons. A receiver operating characteristic (ROC) curve was calculated to determine the sensitivity and specificity of anti-RBD-S1 titers related to clinical benefit

outcomes. The Youden index was applied to identify the optimal cut-point. A Fisher's exact test was used to perform a univariate analysis of the correlation between clinical variables and DCB. We applied the Holm-Bonferroni method [19] to adjust p values while keeping α (0.05) constant for multiple comparisons of clinical-pathological and immune parameters with disease outcomes and immune-related toxicities. A multivariate logistic regression model was performed to estimate the odds ratio (OR) of DCB with a 95% CI as a function of significant variables at univariate analysis. A Mantel-Cox log-rank test was used to compare the survival outcomes of different patient subgroups according to significant variables. Survival curves were visualized through the Kaplan–Meier method. A multivariate Cox regression model was applied to estimate the hazard ratio (HR) with a 95% CI of confirmed significant variables. The Spearman method was used to assess the correlation between anti-RBD-S1 IgG titer log values and duration of both V-TTF and OS. All tests performed were two-sided, and a p value < 0.05 was considered significant. SPSS (IBM SPSS Statistics for Windows, version 23.0, Armonk, NY) and Prism (GraphPad, version 9) software were used for statistical evaluations and figure rendering, respectively.

Results

Patient characteristics and general outcomes

The present analysis included 56 eligible patients who had received their third dose of tozinameran between September 23 and October 7, 2021. The median age was 66 years, and the majority of patients were male (71%). Non-small-cell lung cancer (NSCLC) was the most frequent diagnosis (57%), and all participants had a metastatic extent of disease with an Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0–1. The most common immune checkpoint therapies with PD-1/PD-L1 blocking agents were pembrolizumab (45%) and nivolumab (37%). The median duration of active treatment before and after the booster dose was 8.4 and 4.6 months, respectively. Supplementary Table 1 details the baseline characteristics of the patients. As of the last interim analysis, 11 patients (20%) were still receiving treatment, 45 (80%) have been discontinued, and 19 (34%) have been censored due to no event relevant to survival outcome. We observed 12 PR (21%), 23 SD (41%), 14 (25%) of which lasted more than 6 months, and 21 PD (37%). As a result, DCB and NCB were reported in 26 (46%) and 30 (54%) cases, respectively. The median OS was 26.2 months (95% CI 17.7–34.7) after a median follow-up time of 32.3 months (95% CI 27.4–31.7).

Antibody responses

The third dose of tozinameran resulted in an exponential increase in anti-RBD-S1 IgG titer, the median value of which (714 BAU/mL, 95% CI 179–1271) was significantly higher than the same figures obtained 3 weeks after the first dose (11 BAU/mL, 95% CI 5–19), 8 weeks after the second dose (170 BAU/mL, 95% CI 61–314), and shortly before the booster dosing (32 BAU/mL, 95% CI 21–46; Fig. 1). A ROC curve was calculated to determine the relationship between anti-RBD-S1 IgG titers after the booster dose and DCB. The relative AUC value [0.76 (95% CI 0.63–0.89), $p = 0.001$] was considered valuable in predicting the likelihood of a

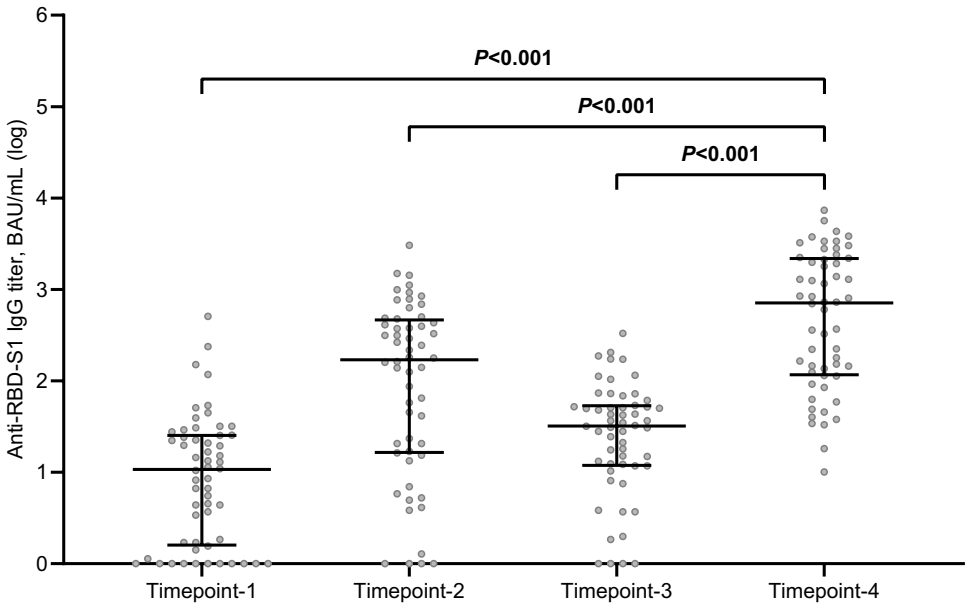

Fig. 1 Longitudinal comparison of scatter plot distributions and medians of antibody titers. *RBD-S1* receptor-binding domain (RBD) of the SARS-CoV-2 Spike protein (S1), *BAU* binding antibody unit; log, logarithmic values. Bars represent median values with interquartile range; timepoint-1 denotes assessment 3 weeks after the first dose of tozinameran; timepoint-2 denotes assessment 8 weeks after the second dose of tozinameran; timepoint-3 denotes assessment before the third dose of tozinameran; timepoint-4 denotes assessment 4 weeks after the third dose of tozinameran

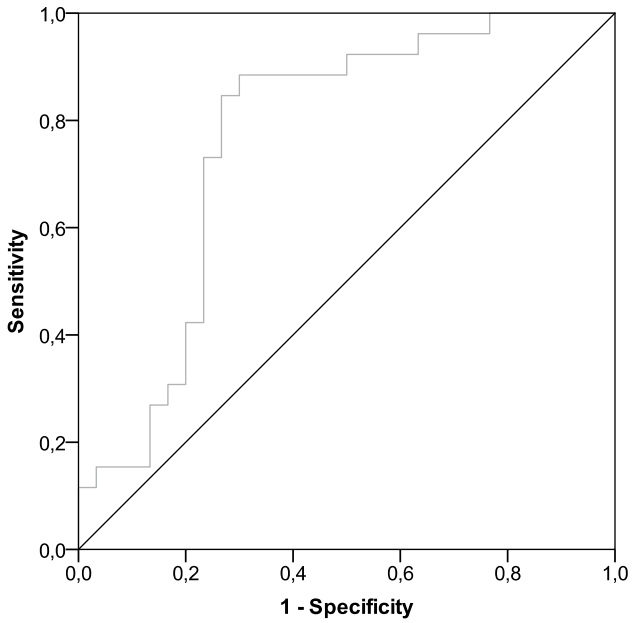

Fig. 2 ROC curve analysis of anti-RBD-S1 IgG titers on DCB. AUC relative value: 0.76 (95% CI 0.63–0.89), $p = 0.001$. *ROC* receiver operating characteristic, *RBD-S1* receptor-binding domain of the SARS-CoV-2 Spike protein, *DCB* durable clinical benefit, *AUC* area under the curve, *CI* confidence interval

positive outcome (Fig. 2). The IgG titer cut-point of 486 BAU/mL was associated with a sensitivity of 0.84 and a specificity of 0.74, allowing a dichotomization of recipients into low-responder (Low-R, < 486 BAU/mL) and high-responder (High-R, ≥ 486 AU/mL) subgroups. Of note, after a median follow-up of 226 days (95% CI 125–525), 13 patients in the Low-R subgroup (50%) and 7 in the High-R subgroup (23.3%, $p = 0.037$) reported contracting SARS-CoV-2 infections, none of which was clinically severe. Computation of the ROC curve in the subgroup of patients with lung cancer confirmed a statistically significant association with DCB [AUC 0.73 (95% CI 0.56–0.90), $p = 0.021$, Supplementary Fig. 1]. Compared to the general population, the same antibody titer (486 BAU/mL) was identified as the optimal cut-point with higher sensitivity (0.91) and specificity (0.77).

Safety

The median interval between the administration of anti-PD-1/PD-L1 agents immediately preceding and following the third dose of tozinameran was 8.5 days (IQR 6–15) and 9.5 days (IQR 6–15), respectively. Before booster vaccination, 18 patients (32%) reported irAEs. Since six patients developed two separate toxicities, we described 24 irAEs, none of which was higher than grade 2. The median time to the first onset of any irAE after the initiation of ICI was 87 days (IQR 29–523). After a median follow-up time of 226 days (IQR 89–565) from booster dosing, irAEs were observed in 13 patients (23%), two of whom experienced severe toxicity (namely, grade 3 thyroiditis and grade 3 vasculitis). Two patients who had previously presented with an irAE developed additional toxicity (grade 2 colitis after grade 2 skin rash and grade 2 arthritis after grade 2 thyroiditis), but we did not observe any flare of irAEs preceding the third dose of tozinameran. A median of 39 days (IQR 21–164) elapsed between the booster dose and the onset of immune-mediated toxicities. On univariate comparison, the overall frequency of irAEs did not differ significantly between ICI exposure before and after the booster dose. Interestingly, the High-R subgroup experienced a significant increase in the cumulative incidence of immuno-related thyroiditis ($p = 0.036$, Table 1). Statistical significance, however, was not maintained after applying correction for multiple testing.

Disease outcomes

In univariate analyses, a diagnosis other than lung cancer ($p = 0.005$), a limited disease burden with a single metastatic site ($p < 0.001$), absence of bone ($p = 0.008$) or liver ($p = 0.025$) involvement, a weight loss ≤ 5% from baseline ($p = 0.001$), and any positive PD-L1 expression ($p < 0.001$) were found to be significantly associated with DCB. The same comparison also revealed a better outcome in favor of the High-R subgroup of patients ($p < 0.001$). In multivariate analysis, the type of cancer diagnosis, extent of disease, PD-L1 expression, and antibody response level after the booster dose retained their predictive significance (Table 2).

As expected, the DCB resulted in a statistically significant improvement in median V-TTF [19.1 months (95% CI 12.8–25.3) vs. 2.0 months (95% CI 1.2–2.8), $p < 0.001$; Supplementary Fig. 2A] and median OS [38.0 months (95% CI 31.5–44.5) vs. 12.5 months (95% CI 10.1–14.9), $p < 0.001$; Supplementary Fig. 2B]. Consistently, univariate survival testing confirmed the variables that significantly correlated with DCB in the multivariate analysis to be significant survival predictors, as all were associated with a lower risk of treatment failure (Table 3, Fig. 3) and mortality (Table 3, Fig. 4). However, only the diagnosis other than lung cancer, burden of disease, and increased humoral response retained their significant potential for V-TTF in multivariate analysis. Cancer type and PD-L1 TPS had an independent impact on OS (Table 3). Furthermore, when these outcomes were evaluated as a function of log anti-RBD-S1 IgG titers, a significant positive linear correlation was found for V-TFF [$\rho = 0.45$ (95% CI 0.21–0.63), $p < 0.001$; Fig. 5A] but not for OS [$\rho = 0.23$ (95% CI −0.05–0.50), $p = 0.076$; Fig. 5B]. The univariate analysis within the subgroup of patients with lung cancer showed a significant benefit in favor of high-responder recipients not only in terms of V-TTF

Table 1 Immune-related adverse events

Adverse event	Before third vaccine dose, N = 56 (100%)		After third vaccine dose, N = 56 (100%)		*P* value	Low-R[a], N = 26 (100%)	High-R[b], N = 30 (100%)	*P* value
	N (%)	CTCAE Grading	N (%)	CTCAE Grading		N (%)	N (%)	
Thyroiditis	8 (14.3%)	1–2	3 (5.3%)	2–3	0.13	2 (7.7%)	9 (30%)	0.036[†]
Skin rash	4 (7.1%)	1–2	1 (1.8%)	2	0.17	2 (7.7%)	3 (10%)	0.76
Pancreatitis	3 (5.3%)	2	1 (1.8%)	2	0.31	3 (11.5%)	1 (3.3%)	0.23
Colitis	3 (5.3%)	2	1 (1.8%)	2	0.31	1 (3.8%)	3 (10%)	0.37
Hepatitis	2 (3.5%)	2	1 (1.8%)	2	0.56	1 (3.8%)	2 (6.6%)	0.63
Pneumonitis	2 (3.5%)	2	–	–	0.15	–	2 (6.6%)	0.17
Arthritis	2 (3.5%)	1–2	2 (3.5%)	2	1.00	2 (7.7%)	2 (6.6%)	0.88
Myositis	–	–	1 (1.8%)	2	0.31	–	1 (3.3%)	0.34
Vasculitis	–	–	1 (1.8%)	3	0.31	1 (3.8%)	–	0.27
Uveitis	–	–	1 (1.8%)	2	0.31	–	1 (3.3%)	0.34

CTCAE common terminology criteria for adverse events, version 5.0

[a]Low-R indicates the subgroup of patients with an anti-RBD-S1 IgG titer < 486 BAU/mL after the third dose of vaccine

[b]High-R indicates the subgroup of patients with an anti-RBD-S1 IgG titer ≥ 486 BAU/mL after the third dose of vaccine,

[†]Statistical significance not maintained after Holm-Bonferroni *p* value correction for multiple comparisons

[8.4 months (95% CI 3.1–23.2) vs. 1.9 months (95% CI 1.0–3.7), $p < 0.001$; Supplementary Fig. 3A] but also OS [30.4 months (95% CI 9.3–51.5) vs. 12.0 months (95% CI 9.1–14.8), $p = 0.014$; Supplementary Fig. 3B].

Discussion

The extensive deployment of COVID-19 vaccination has raised new concerns about clinical interactions between active antiviral immunization and immunologic therapies [20]. Since the third dose of tozinameran is expected to maximize the humoral and cellular immune responses [21, 22], its impact on cancer patients receiving ICI-based treatments warrants special attention. In this research, we investigated the specific safety and disease outcomes of patients treated with agents targeting the immunoregulatory PD-1/PD-L1 axis for a wide range of advanced solid malignancies over a 18-month period following booster dosing. Although longitudinal assessment of humoral responses confirmed a significant increase in antibody titers after the third dose, we observed no difference in the frequency of irAEs. However, it is noteworthy that recipients who demonstrated a more sustained antibody response had an increased incidence of moderate to severe immune-related thyroiditis. The same patients also appear to benefit from improved time-to-event outcomes as a result of a lower risk of loss of disease control and death. The fact that, to the best of our knowledge, similar findings have not been previously reported requires a critical assessment of their clinical relevance.

Because COVID-19 vaccination might elicit hyperstimulation of T-cell and dendritic cell functions [23] and increased cytokine release [13, 24], concomitant treatment with ICIs has been considered a risk factor for developing severe irAE. After initial evidence of a favorable short-term safety profile in this group of patients [10], a subsequent prospective study confirmed a low rate of severe irAEs in mRNA-1273 vaccine recipients receiving ICIs with or without cytotoxic chemotherapy [25]. Our prospective assessment indicates an incidence of any grade immune-related toxicities within the expected range [26], with no increase after the booster dose of the vaccine. In addition, the median time to irAE development and lack of exacerbation of previous toxicities are consistent with the results of several retrospective series addressing these aspects of ICI treatment after the second or third dose [27–31]. The apparent increase in the frequency of thyroiditis was relatively unexpected because it has already been described as an autoimmune disorder associated with SARS-CoV-2 infections [32]. Although not confirmed by statistical testing for multiple comparisons, we observed an associative trend between immune-related thyroiditis and the magnitude of antibody response. The evidence on thyroid dysfunction resulting from COVID-19 vaccination is still controversial, as it mainly relies on low-rated meta-analytic appraisals of data from non-cancer patients [33, 34]. Our findings suggest a potential interaction between vaccination and treatment with anti-PD-1/PD-L1 agents. The

Table 2 Correlation between clinical-pathological variables and clinical benefit outcome

	Univariate analysis			Multivariate analysis	
	NCB N = 30 (100%)	DCB N = 26 (100%)	*P* value	OR (95% CI)	*P* value
Age			0.99	–	–
≤ 70 years (N = 32)	17 (56.7%)	15 (57.7%)			
> 70 years (N = 24)	13 (43.3%)	11 (43.3%)			
Sex			0.55	–	–
Female (N = 16)	10 (33.3%)	6 (23.1%)			
Male (N = 40)	20 (66.7%)	20 (76.9%)			
ECOG PS			0.25	–	–
0 (N = 17)	7 (23.3%)	10 (38.5%)			
1 (N = 39)	23 (76.7%)	16 (61.5%)			
Cancer type			0.005†		0.021
Others (N = 19)	5 (16.7%)	14 (53.8%)		1.00	
Lung (N = 37)	25 (83.3%)	12 (46.2%)		0.04 (0.01–0.61)	
Number of metastatic sites			< 0.001†		0.038
1 (N = 23)	4 (13.3%)	19 (73.1%)		1.00	
≥ 2 (N = 33)	26 (86.7%)	7 (26.9%)		0.08 (0.01–0.86)	
CNS metastases			0.34	–	–
No (N = 44)	22 (73.3%)	22 (84.6%)			
Yes (N = 12)	8 (26.7%)	4 (15.4%)			
Bone metastases			0.008†		0.536
No (N = 39)	16 (53.3%)	23 (88.5%)		1.00	
Yes (N = 17)	14 (46.7%)	3 (11.5%)		0.43 (0.03–5.99)	
Liver metastases			0.025	–	–
No (N = 50)	24 (80.0%)	26 (100%)			
Yes (N = 6)	6 (20.0%)	–			
Weight loss			0.001†		0.254
< 5% (N = 39)	15 (50.0%)	24 (93.2%)		1.00	
≥ 5% (N = 17)	15 (50.0%)	2 (7.7%)		0.19 (0.01–3.29)	
PD-L1 TPS			< 0.001†		0.004
< 1% or unknown (N = 22)	20 (66.7%)	2 (7.7%)		1.00	
≥ 1% (N = 34)	10 (33.3%)	24 (93.3%)		49.65 (3.49–> 100)	
Treatment setting			0.26	–	–
First line (N = 36)	17 (56.7%)	19 (73.1%)			
Second or later line (N = 20)	13 (43.3%)	7 (26.9%)			
Corticosteroid therapy[a]			0.34	–	–
No (N = 44)	22 (73.3%)	22 (84.6%)			
Yes (N = 12)	8 (26.7%)	4 (15.4%)			
ICI therapy			0.48	–	–
Anti-PD-1 (N = 47)	24 (80.0%)	23 (88.5%)			
Anti-PD-L1 (N = 9)	6 (20.0%)	3 (11.5%)			
Antibody response[b]			< 0.001†		0.005
Low-R (N = 26)	22 (73.3%)	4 (15.4%)		1.00	
High-R (N = 30)	8 (26.7%)	22 (84.6%)		49.45 (3.27–> 100)	

NCB no clinical benefit, *DCB* durable clinical benefit, *OR* odds ratio, *CI* confidence interval, *ECOG PS* eastern cooperative oncology group performance status, *CNS* central nervous system, *PD-L1 TPS* programmed cell death-ligand 1 tumor proportion score, *ICI* immune checkpoint inhibitor

[a]corticosteroid therapy indicates ≥ 10 mg prednisone equivalent daily for at least 7 days in the 28 days preceding the third dose of vaccine

[b]Low-R indicates the subgroup of patients with an anti-RBD-S1 IgG titer < 486 BAU/mL after the third dose of vaccine, High-R indicates the subgroup of patients with an anti-RBD-S1 IgG titer ≥ 486 BAU/mL after the third dose of vaccine

†Statistical significance maintained after Holm-Bonferroni *p* value correction for multiple comparisons

Table 3 Analysis of survival

Variable	Vaccine-related time-to-treatment failure				Overall survival			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	Median V-TTF (95% CI), months	*P* value	HR (95% CI)	*P* value	Median OS (95% CI), months	*P* value	HR (95% CI)	*P* value
Cancer type		0.006		0.005		0.005		0.019
Others	9.8 (2.3–17.3)		1.00		38.0 (27.5–48.5)		1.00	
Lung	2.7 (1.8–3.6)		2.77 (1.36–5.64)		14.9 (11.4–18.3)		2.79 (1.18–6.62)	
Number of metastatic sites		< 0.001		0.026		< 0.001		0.121
− 1	19.1 (7.8–30.3)		1.00		26.2 (23.8–NR)		1.00	
≥ 2	2.7 (1.7–3.7)		2.44 (1.11–5.31)		14.7 (12.4–17.0)		2.27 (0.80–6.39)	
PD-L1 TPS		0.001		0.167		< 0.001		0.04
< 1% or unknown	9.4 (4.0–14.8)		1.00		12.4 (9.6–15.2)		1.00	
≥ 1%	2.5 (1.0–3.9)		0.62 (0.31–1.22)		38.0 (26.3–49.8)		0.46 (0.22–0.96)	
Antibody response[a]		< 0.001		< 0.001		< 0.001		0.261
Low-R	2.3 (1.5–3.2)		1.00		12.4 (8.0–16.9)		1.00	
High-R	12.2 (3.5–20.9)		0.25 (0.12–0.52)		35.3 (13.4–57.1)		0.62 (0.28–1.41)	

HR hazard ratio, *CI* confidence interval, *PD-L1* TPS, programmed cell death-ligand 1 tumor proportion score, *NR* not reached

[a]Low-R indicates the subgroup of patients with an anti-RBD-S1 IgG titer < 486 BAU/mL after the third dose of vaccine, High-R indicates the subgroup of patients with an anti-RBD-S1 IgG titer ≥ 486 BAU/mL after the third dose of vaccine

unavailability of measuring anti-thyroid antibodies before and after the third immunization, as well as the impossibility of comparison with a control group of unvaccinated patients, does not allow further insights to be drawn [35].

The clinical effects of SARS-CoV-2 vaccination on the efficacy of ICI-based therapies are currently unknown. However, the complex relationship between vaccine adaptive responses and immune checkpoint blockade has raised concerns about a potential increase in tumor hyper-progression [36]. This paradoxical phenomenon has been related to the diffuse infiltration of metastatic sites by activated lymphocytes as a result of enhanced effects of the vaccination itself [37]. In this regard, two retrospective studies reported that influenza vaccination could even provide an advantage in terms of overall survival, ruling out the generic risk of hyper-progression associated with active antiviral immunization during ICI exposure [38, 39]. Similarly, a retrospective review of advanced cancer patients on PD-1 blockade who received seasonal flu vaccine reported no increase in incidence or severity of irAEs within 2 months of treatment [40]. Nonetheless, because COVID-19 vaccination may elicit less predictable immune responses than influenza vaccines, the threat of a detrimental effect on disease outcome cannot be overlooked. A large retrospective study showed that the clinical benefit of the anti-PD-1 agent camrelizumab has improved in the subgroup of patients who received the SARS-CoV-2 BBIPB-CorV vaccine compared with unvaccinated counterparts [41]. Despite significant differences in methodology, our results appear to be consistent with the described evidence, implying that COVID-19 vaccination does not reduce the clinical efficacy of PD-1/PD-L1 targeting agents. Similar to previous studies, we did not observe any cases of hyper-progression nor did the rate of loss of disease control differ from what was expected before the third dose of tozinameran. Although the unavoidability of SARS-CoV-2 vaccination during COVID-19 outbreaks precluded a direct comparison with unvaccinated patients, we observed a significant survival advantage in favor of high-level responders. Furthermore, the survival benefit observed in the subgroup of patients with advanced lung cancer who exhibited an enhanced antibody response seems to confirm previous insights.

The current study acknowledges several shortcomings, including but not limited to the following issues. The Vax-On-Third, like all others of its kind, was designed to enroll large numbers of patients in a short time frame. While the need to address COVID-19-related emergency may explain such an approach, this "all-comers" recruitment did not allow for adequate stratification of participants, making the study prone to selection bias. We included a wide variety of malignancies, implying that different interactions between vaccination and ICIs cannot be ruled out among

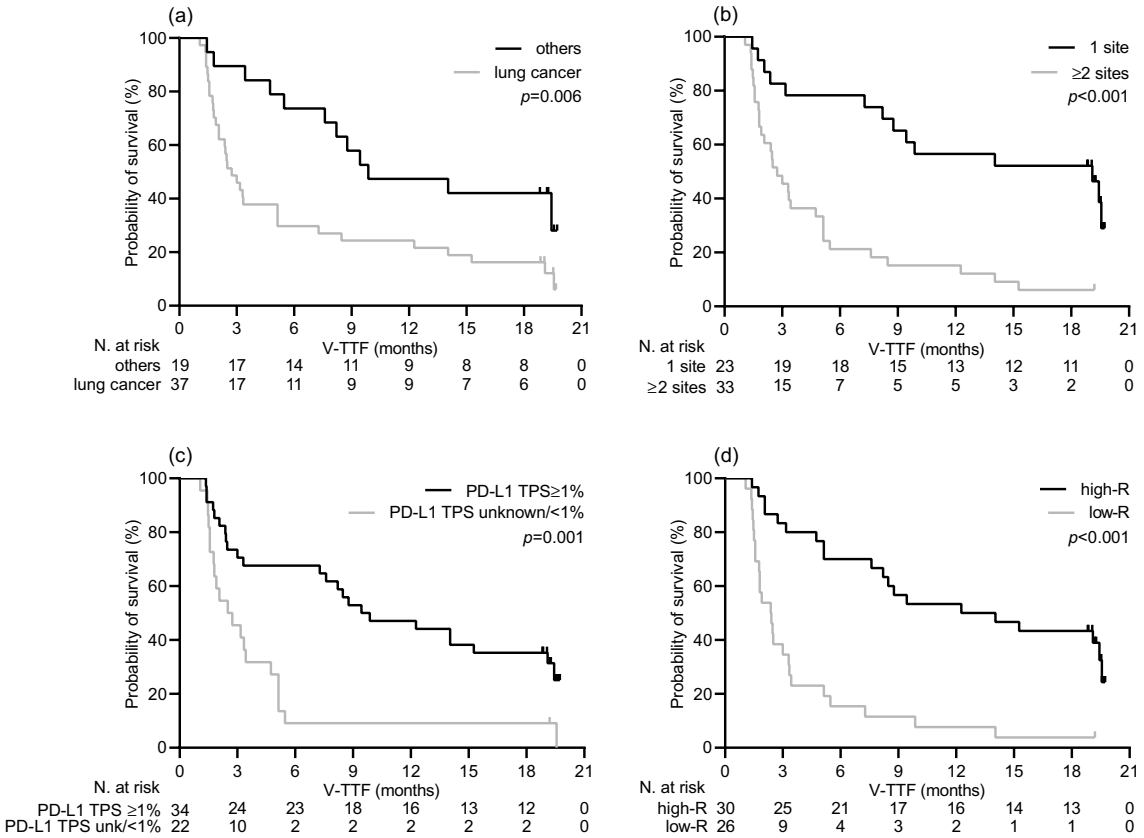

Fig. 3 Vaccine-related time-to-treatment failure depending on significant clinical variables. **a** type of cancer diagnosis: others versus lung cancer; **b** metastatic extent of disease: 1 site versus ≥ 2 sites; **c** programmed cell death-ligand 1 tumor proportion score (PD-L1 TPS): ≥ 1% versus unknown or < 1%; **d** level of antibody response: Low-R (subgroup of patients with an anti-RBD-S1 IgG titer < 486 BAU/mL after the third dose of vaccine) versus High-R (subgroup of patients with an anti-RBD-S1 IgG titer ≥ 486 BAU/mL after the third dose of vaccine)

patients with different types of cancer. The specific design of the present research also has an inherent immortal-time bias, which results from the lapse between initiation of ICI treatment and vaccination, potentially leading to an overestimate of the survival benefit [42]. The lack of a linear correlation between antibody titers and duration of overall survival, which has otherwise been reported for time-to-treatment failure, is consistent with the latter consideration. In addition, we did not provide an independent radiological review or immune-related evaluation of treatment response [43]. These flaws may have led to an incorrect assessment of anti-PD-1/PD-L1 agent activity and V-TTF duration. Finally, despite being overlapped with those of similar studies, the sample size of this series is small, as is the median duration of follow-up, which is relatively short. The last issues emphasize that multivariable statistical comparisons may amplify false-positive results, the significance of which should be therefore considered exploratory.

In conclusion, many areas of uncertainty remain in cancer patients receiving ICIs with regard to the third dose of COVID-19 vaccination. We have investigated the effects of antibody response in this condition for the first time. Our results demonstrate a favorable clinical interaction leading improved disease outcomes. Although the limited sample size of this study, as well as the complexity and variability of mechanisms underlying the development of irAEs [44], does not allow us to rule out rare interactions with tozinameran booster dosing, our findings suggest that the risk of severe immune toxicities on PD-1/PD-L1 blockade is likely small. The increased incidence of specific adverse events associated with both vaccination and treatment, including autoimmune thyroiditis, implies that all these patients should be closely monitored. These results would strengthen the recommendation that anti-PD-1/

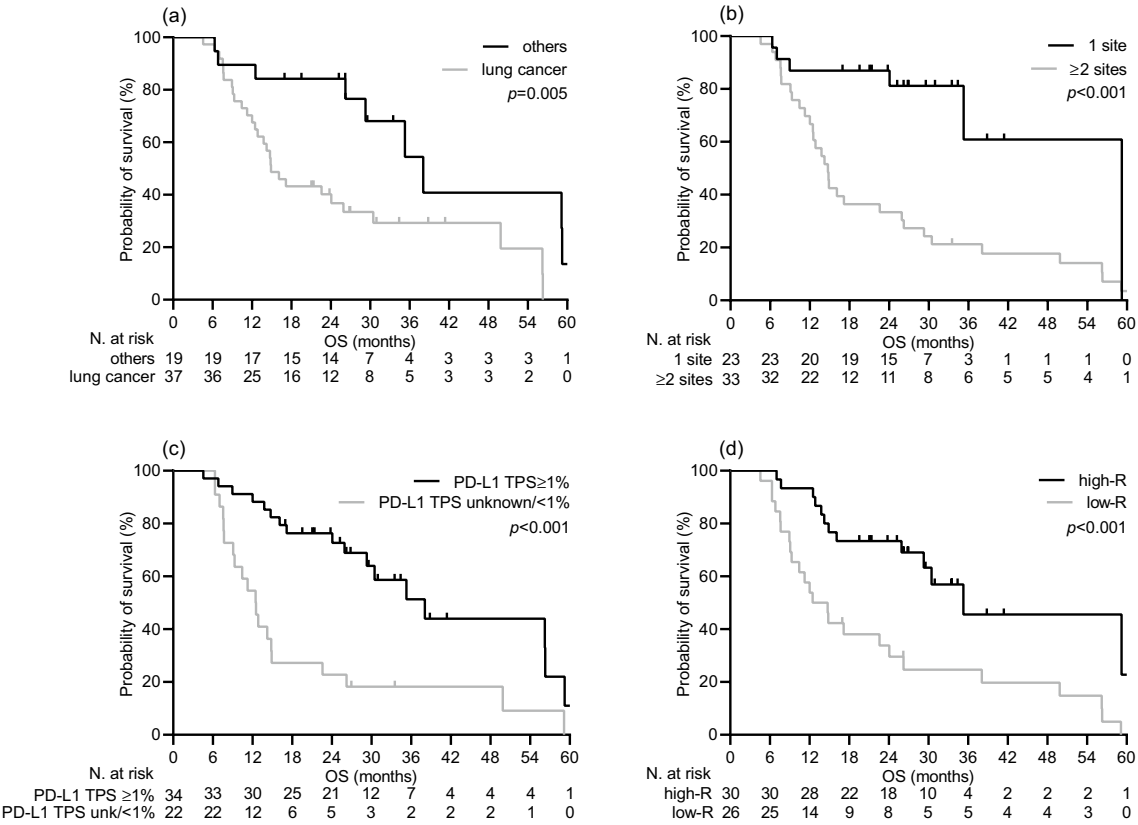

Fig. 4 Overall survival depending on significant clinical variables. **a** type of cancer diagnosis: others versus lung cancer; **b** metastatic extent of disease: 1 site versus ≥ 2 sites; **c** programmed cell death-ligand 1 tumor proportion score (PD-L1 TPS): ≥ 1% versus unknown or < 1%; **d** level of antibody response: Low-R (subgroup of patients with an anti-RBD-S1 IgG titer < 486 BAU/mL after the third dose of vaccine) versus High-R (subgroup of patients with an anti-RBD-S1 IgG titer ≥ 486 BAU/mL after the third dose of vaccine)

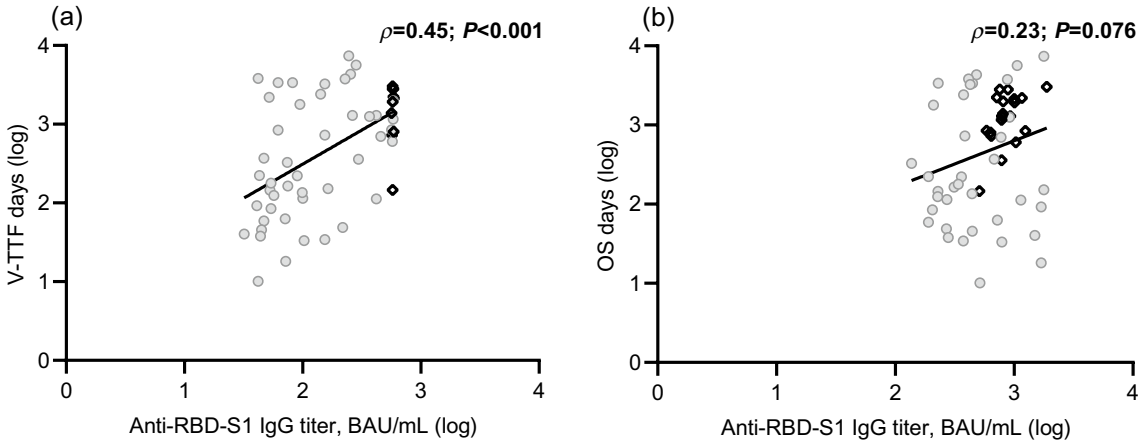

Fig. 5 Scatter plot of survival by anti-RBD-S1 IgG titers. **a** Vaccine-related time-to-treatment failure and **b** overall survival. Abbreviations: RBD-S1, receptor-binding domain (RBD) of the SARS-CoV-2 Spike protein (S1); BAU, Binding Antibody Unit; log, logarithmic values. Circle-shaped marks indicate cases that experienced survival-relevant events; rhombus-shaped marks indicate censored cases

PD-L1 treatment plans should not be altered depending on immunization schedules [45]. The limitations of the study and the lack of reliable comparisons indicate that these results have hypothesis-generating potential, which should be confirmed in independent prospective cohorts.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00262-023-03489-1.

Author contributions FN and EMR designed the study and wrote the manuscript. DG performed the statistical analysis. AF, JRGB, AV, EM, CF, MS, CS, MGC, and FP enrolled the patients, collected clinical and laboratory data and setup the database. VP, GT, and MAS performed serological testing, and contributed to the interpretation of the data. All authors discussed the results and critically revised the manuscript. All authors read and approved the final manuscript.

Funding This research did not receive any specific grant from agencies in the public, commercial, or not-for-profit sectors and no sources of funding were used to assist in the preparation of this manuscript.

Data availability The datasets generated and analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

Ethics approval This study was approved by the referring Ethics Committee (Comitato Etico Lazio1, Rome, Italy; protocol number: 1407/CE Lazio1). All patients were required to provide written informed consent before participating in this study. All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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