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Impact of concomitant medication on clinical outcomes in patients with advanced non-small cell lung cancer treated with immune checkpoint inhibitors: A retrospective study

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Abstract

Background: It has recently been suggested that concomitant medication may affect the clinical outcome of patients treated with immune checkpoint inhibitors (ICIs). However, only a few studies on the impact of concomitant medication on immune-related adverse events (irAEs) have previously been reported. Here, we aimed to determine the impact of concomitant medication on the efficacy and safety of ICIs.

Methods: We retrospectively analyzed the data of 300 patients treated with nivolumab or pembrolizumab for advanced non-small cell lung cancer (NSCLC) between January 2016 and July 2018. Multivariate logistic regression analysis was used to assess the effect of concomitant medication on treatment response or irAEs. A multivariate Cox proportional hazards model was used to evaluate concomitant medication-related factors associated with time-to-treatment failure or overall survival (OS).

Results: A total of 70 patients responded to treatment and 137 experienced irAEs. The response rate and incidence of irAEs in patients treated with ICIs were not significantly associated with concomitant medication. Multivariate analysis showed that the use of opioids was an independent factor (time-to-treatment failure: hazard ratio 1.39, p = 0.021, OS: hazard ratio 1.54, p = 0.007).

Conclusions: The efficacy and safety of nivolumab or pembrolizumab in the treatment of patients with advanced NSCLC were not significantly influenced by concomitant medication. However, opioid usage might be associated with shorter OS in patients treated with these ICIs. Further mechanistic investigations should explore whether these associations are purely prognostic or contribute to ICI resistance.

KEYWORDS
concomitant medication, immune checkpoint inhibitors, immune-related adverse events, non-small cell lung cancer, opioids

INTRODUCTION

Lung cancer has the highest mortality rate among all cancer types worldwide.[1] Treatment for advanced non-small cell lung cancer (NSCLC) is selected based on the expression of the driver oncogene, programmed death-ligand 1 (PD-L1), and other factors.[2] Immune checkpoint inhibitors (ICIs), such as nivolumab, pembrolizumab, and atezolizumab, which block the programmed cell death protein 1 (PD-1)/PD-L1 pathway in the immune system, have been approved for use

in patients with advanced NSCLC. ICIs restore the antitumor activity of T cells and have received attention as an alternative treatment strategy to chemotherapy. However, only about 20% of patients respond to ICI monotherapy.[3] The efficacy of ICIs has been reported to be influenced by various factors, such as PD-L1 expression, history of smoking, Eastern Cooperative Oncology Group Performance Status (ECOG PS),[4] and radiotherapy.[5–7] Furthermore, it has been reported that concomitant medication may affect the efficacy of ICIs.[8–17]

In this regard, immunomodulatory effects have been reported for medications that are used in the treatment of common diseases, such as hyperlipidemia, diabetes, and hypertension.[10] The concurrent use of statins has been associated with an improved response and longer time-to-treatment failure (TTF) in patients treated with nivolumab for advanced NSCLC.[11] In patients treated with ICIs for metastatic malignant melanoma and advanced NSCLC, progression-free survival (PFS) and overall survival (OS) tend to be longer in those who used metformin concomitantly, without an increase in adverse events.[16,17] In vivo, fibrates, dipeptidyl peptidase-4 (DPP-4) inhibitors, and angiotensin receptor blockers (ARBs) have been shown to have a synergistic influence on the antitumor effect of ICIs.[18–20] In addition, the activities of the gut microbiota have been linked to the efficacy of ICIs.[21] It has been reported that the concomitant use of medications such as antibiotics and proton pump inhibitors (PPIs), may influence the outcome of treatment with ICIs, by affecting gut microbiota.[12]

Regarding drug safety, it is known that immune-related adverse events (irAEs) mimicking autoimmune disorders, are caused by treatment with ICIs.[22] Moreover, irAEs result from the activation of the immune system outside of the tumor microenvironment, which can occur in any organ.[23] It has also been reported that the occurrence of irAEs during treatment with ICIs is associated with a high therapeutic effect.[24] However, only the impact of the concomitant use of metformin on the occurrence of irAEs has been previously studied.[16,17] The purpose of this study was to clarify the impact of concomitant medication on the clinical outcomes of ICI treated patients with NSCLC.

METHODS

Patient data collection

We retrospectively collected the data of 304 patients treated with nivolumab or pembrolizumab for advanced NSCLC at the National Cancer Center Hospital East, between January 2016 and July 2018, from their medical records. The study protocol was approved by the Ethics Committee of the National Cancer Center (Approval No. 2018-348). The ethics committee waived the requirement for informed consent due to the retrospective study design. As this study was a retrospective analysis of de-identified data, written informed consent was not required. The following clinical factors were examined at the beginning of nivolumab or pembrolizumab therapy: age, sex, ECOG PS, histological

TABLE 1 Patient characteristics and concomitant medications

Factors	$n = 300$	%
Age, years (median [range])	65 (31–82)	
Sex		
Male	226	75.3
Female	74	24.7
ECOG PS		
0/1	65/181	82.0
2/3/4	51/2/1	18.0
Histological types		
Adenocarcinoma	189	63.0
Squamous cell carcinoma	74	24.7
Others	37	12.3
EGFR mutation		
Mutant	36	12.0
PD-L1 expression		
≧50%	67	22.3
1–49%	47	15.7
<1%	23	7.7
Unknown	163	54.3
PD-L1 monotherapy		
Nivolumab	203	67.7
Pembrolizumab	97	32.3
Lines of chemotherapy	2 (1–11)	
1	40	13.3
2	122	40.7
3/4/5/6/7/9/11	64/35/27/7/3/1/1	46.0
Smoking status		
Current or former	250	83.3
Never	50	16.7
History of radiotherapy		
Yes	156	52.0
Concomitant medications	**n**	**%**
Statins	26	8.7
Fibrates	3	1.0
DPP-4 inhibitors	22	7.3
Metformin	8	2.7
ARBs	40	13.3
Corticosteroids	12	4.0
Antibiotics	14	4.7
Probiotics	14	4.7
NSAIDs	140	46.7
PPIs	163	54.3
Opioids	114	38.0
Laxatives	101	33.7
Vitamin D	58	19.3

Abbreviations: ARBs, angiotensin receptor blockers; DPP-4, dipeptidyl peptidase-4; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EGFR, epidermal growth factor receptor; NSAIDs, nonsteroidal anti-inflammatory drugs; PD-L1, programmed death-ligand 1; PPIs, proton pump inhibitors.

TABLE 2 Univariate and multivariate analyses of variable factors of response

Characteristic	RR (%)	Univariate analysis			Multivariate analysis		
		OR	95% CI	p-value	OR	95% CI	p-value
Age, years							
≧70	21.8	0.76	0.43–1.34	0.334			
<70	27.0						
Sex							
Male	23.9						
Female	21.6	0.88	0.47–1.65	0.688			
ECOG PS							
0 or 1	24.0	1.23	0.60–2.54	0.570			
2, 3, or 4	20.4						
Histology							
Squamous	12.2	0.38	0.18–0.80	0.009	3.17	1.43–7.05	0.005
Nonsquamous	27.0						
EGFR mutation							
Yes	13.9	0.49	0.18–1.32	0.153	2.08	0.74–5.90	0.167
No	24.6						
Line of chemotherapy							
1	45.0			0.001	3.91	1.71–8.94	0.001
2	24.6				1.97	1.03–3.77	0.040
≧3	15.9						
Smoking status							
Current or former	23.6	1.10	0.53–2.27	0.807			
Never	22.0						
History of radiotherapy							
Yes	20.5	0.72	0.42–1.23	0.229			
No	26.4						
Use of statins							
Yes	11.5	0.40	0.12–1.39	0.137	3.00	0.82–10.92	0.096
No	24.5						
Use of fibrates							
Yes	33.3	1.65	0.15–18.5	0.551[a]			
No	23.2						
Use of DPP-4							
Yes	31.8	1.59	0.62–4.08	0.328			
No	22.7						
Use of metformin							
Yes	37.5	2.02	0.47–8.65	0.395[a]			
No	22.9						
Use of ARBs							
Yes	25.0	1.11	0.51–2.40	0.789			
No	23.1						
Use of corticosteroids							
Yes	16.7	0.65	0.14–3.03	0.739[a]			
No	23.6						
Use of antibiotics							
Yes	21.4	0.89	0.24–3.29	1.000[a]			
No	23.4						

(Continues)

T A B L E 2 (Continued)

Characteristic	RR (%)	Univariate analysis			Multivariate analysis		
		OR	95% CI	*p*-value	OR	95% CI	*p*-value
Use of probiotics							
Yes	21.4	0.89	0.24–3.29	1.000[a]			
No	23.4						
Use of NSAIDs							
Yes	18.6	0.60	0.35–1.04	0.068	1.59	0.82–10.92	0.172
No	27.5						
Use of PPIs							
Yes	19.6	0.64	0.37–1.09	0.098	0.97	0.50–1.88	0.936
No	27.7						
Use of opioids							
Yes	17.5	0.58	0.32–1.04	0.063	1.62	0.83–3.17	0.162
No	26.9						
Use of laxatives							
Yes	15.8	0.51	0.27–0.94	0.029	1.29	0.63–2.64	0.482
No	27.1						
Use of vitamin D							
Yes	17.2	0.63	0.30–1.33	0.222			
No	24.8						

Abbreviations: ARBs, angiotensin receptor blockers; CI, confidence interval; DPP-4, dipeptidyl peptidase-4; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EGFR, epidermal growth factor receptor; NSAIDs, nonsteroidal anti-inflammatory drugs; OR, odds ratio; PPIs, proton pump inhibitors; RR, response rate.
[a]Fisher's exact test.

types, epidermal growth factor receptor mutation (EGFR), PD-L1 expression, line of chemotherapy, smoking status, history of radiation, and use of concomitant medications. The concomitant medications investigated included statins, fibrates, DPP-4 inhibitors, metformin, ARBs, corticosteroids, antibiotics, probiotics, PPIs, nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, laxatives, and vitamin D. Medications used only as required, for example, painkillers and laxatives, were not included. Clinical follow-up including physical examination, chest radiography, and routine laboratory tests were performed at least every four weeks. Computed tomography was performed at regular intervals according to local standards. The overall response was determined as stated by the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.[25] In this study, irAEs were identified as adverse events associated with nivolumab or pembrolizumab use and were graded based on the American Society of Clinical Practice guidelines[24] or the Common Terminology Criteria for Adverse Events v4.0.[26]

Statistical analysis

To evaluate the efficacy of nivolumab or pembrolizumab, patients were divided into responders and nonresponders. Responders were defined as patients who achieved a complete response (CR) or partial response (PR), as stated by the RECIST v1.1.[25] Comparison of categorical variables between responders and nonresponders was performed using the chi-squared or Fisher's exact test, where appropriate. Categorical variables between the groups with irAEs and without irAEs were compared using the chi-squared or Fisher's exact test, where appropriate. Multivariate logistic regression analysis was used to assess the factors affecting response or the occurrence of irAEs. Factors included in the multivariate analysis were those with *p*-values <0.2 in the univariate analysis.

TTF was defined as the period from the date of nivolumab or pembrolizumab treatment initiation to the date of treatment discontinuation because of disease progression, death, or severe adverse events. OS was defined as the period from the date of nivolumab or pembrolizumab treatment initiation to the date of patient's death, irrespective of the cause. TTF and OS were censored on the day of data cutoff (i.e., May 31, 2019), and were estimated using Kaplan–Meier curves with a two-sided log-rank test. A multivariate Cox proportional hazards model was used to evaluate factors with *p*-values <0.2.

Two-sided *p*-values <0.05 were considered statistically significant. All statistical analyses were performed using the Statistical Package for the Social Sciences v22.0 (IBM Corp.).

RESULTS

Patient characteristics

In total, 304 patients were treated with nivolumab (3 mg/kg each cycle) or pembrolizumab (200 mg/bodyweight each cycle) for advanced NSCLC. Four patients with incomplete
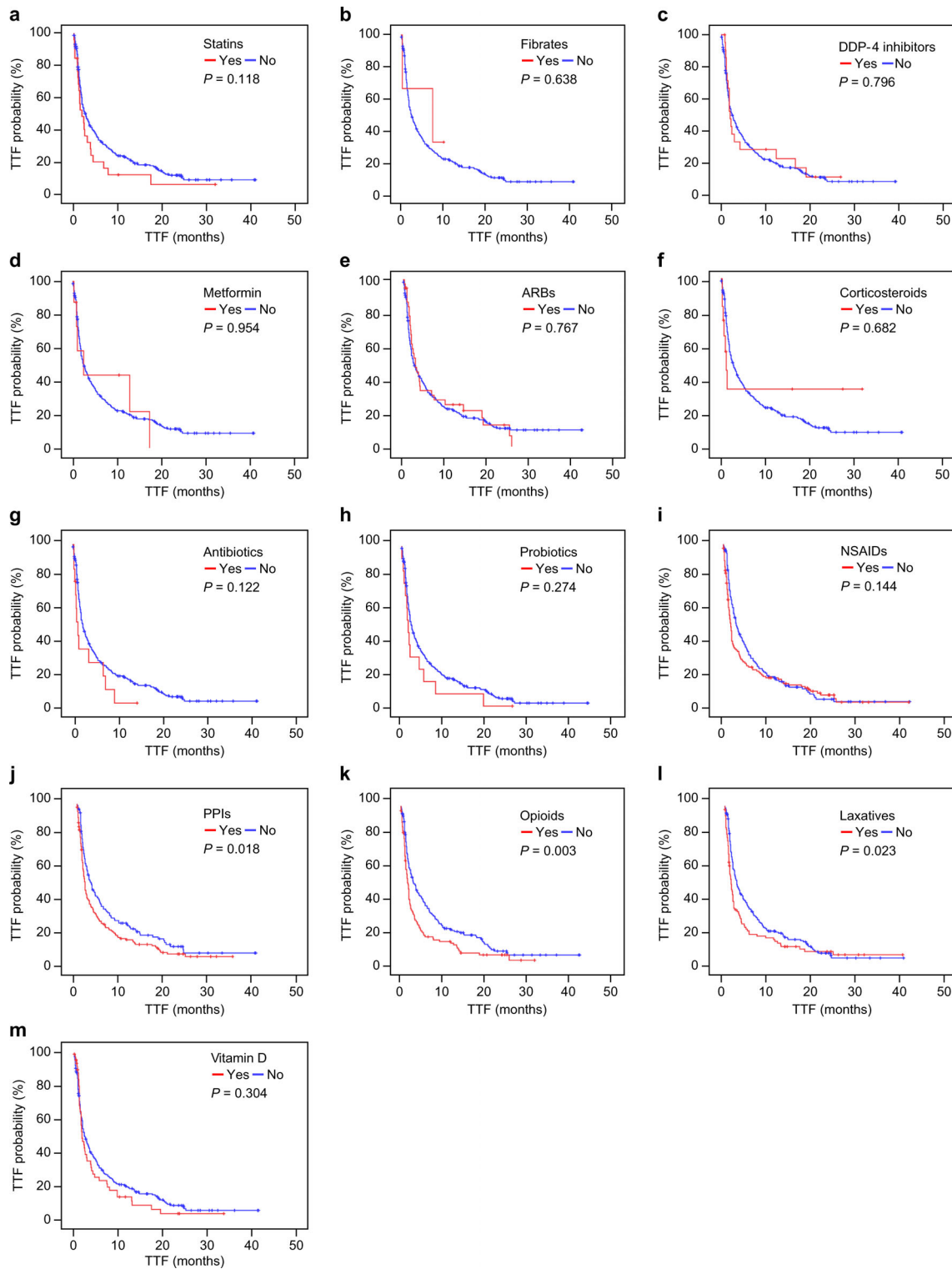
FIGURE 1 Kaplan–Meier curves of time-to-treatment failure (TTF) with or without concomitant medication. TTF was not significantly different with (red lines) or without (blue lines) each concomitant medication. (a) TTF with or without statins (median TTF: 1.9 vs. 2.8 months, log-rank $p = 0.118$); (b) TTF with or without fibrates (median TTF: 7.5 vs. 2.5 months, log-rank $p = 0.638$); (c) TTF with or without dipeptidyl peptidase-4 (DPP-4) inhibitors (median TTF: 2.1 vs. 2.6 months, log-rank $p = 0.796$); (d) TTF with or without metformin (median TTF: 2.5 vs. 2.5 months, log-rank $p = 0.954$); (e) TTF with or without angiotensin receptor blockers (ARBs) (median TTF: 2.8 vs. 2.4 months, log-rank $p = 0.767$); (f) TTF with or without corticosteroids (median TTF: 1.2 vs. 2.6 months, log-rank $p = 0.682$); (g) TTF with or without antibiotics (median TTF: 1.2 vs. 2.6 months, log-rank $p = 0.122$); (h) TTF with or without probiotics (median TTF: 1.5 vs. 2.6 months, log-rank $p = 0.274$); (i) TTF with or without nonsteroidal anti-inflammatory drugs (NSAIDs) (median TTF: 1.8 vs. 3.3 months, log-rank $p = 0.144$); (j) TTF with or without proton pump inhibitors (PPIs) (median TTF: 1.9 vs. 3.5 months, log-rank $p = 0.018$); (k) TTF with or without opioids (median TTF: 1.8 vs. 3.5 months, log-rank $p = 0.003$); (l) TTF with or without laxatives (median TTF: 1.6 vs. 3.2 months, log-rank $p = 0.023$); (m) TTF with or without vitamin D (median TTF: 1.9 vs. 2.8 months, log-rank $p = 0.304$)
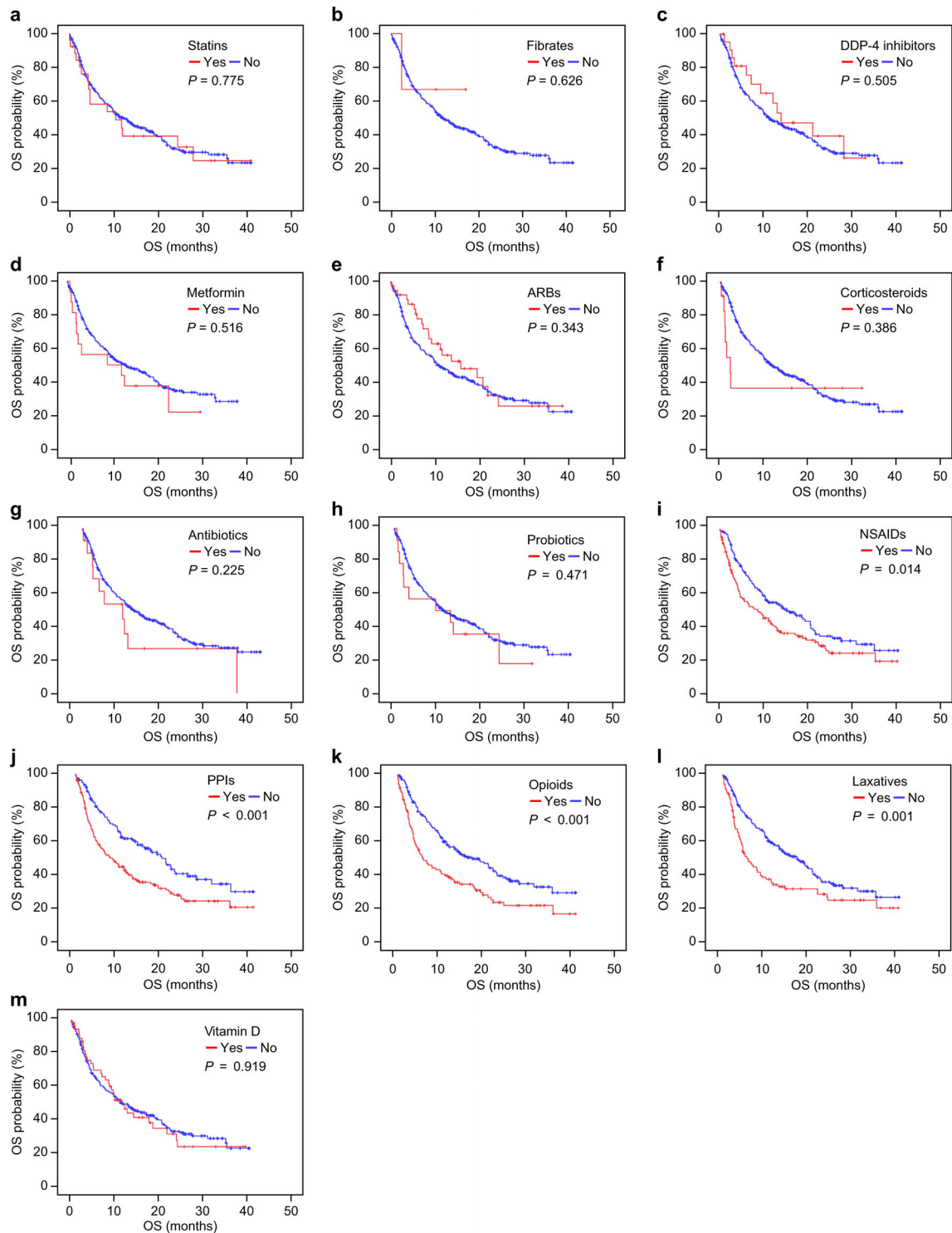
FIGURE 2 Kaplan–Meier curves of overall survival (OS) with or without concomitant medication. OS was not significantly different with (red lines) or without (blue lines) each concomitant medication. (a) OS with or without statins (median OS: 10.5 vs. 11.7 months, log-rank $p = 0.775$); (b) OS with or without fibrates (median OS: No data vs. 11.7 months, log-rank $p = 0.626$); (c) OS with or without dipeptidyl peptidase-4 (DPP-4) inhibitors (median OS: 13.8 vs. 11.3 months, log-rank $p = 0.505$); (d) OS with or without metformin (median OS: 12.9 vs. 11.7 months, log-rank $p = 0.516$); (e) OS with or without angiotensin receptor blockers (ARBs) (median OS: 15.9 vs. 10.9 months, log-rank $p = 0.343$); (f) OS with or without corticosteroids (median OS: 2.3 vs. 11.8 months, log-rank $p = 0.386$); (g) OS with or without antibiotics (median OS: 9.3 vs. 12.0 months, log-rank $p = 0.225$); (h) OS with or without probiotics (median OS: 9.7 vs. 11.7 months, log-rank $p = 0.471$); (i) OS with or without nonsteroidal anti-inflammatory drugs (NSAIDs) (median OS: 8.8 vs. 15.9 months, log-rank $p = 0.014$); (j) OS with or without proton pump inhibitors (PPIs) (median OS: 7.9 vs. 19.6 months, log-rank $p < 0.001$); (k) OS with or without opioids (median OS: 5.7 vs. 15.9 months, log-rank $p < 0.001$); (l) OS with or without laxatives (median OS: 5.6 vs. 17.3 months, log-rank $p = 0.001$); (m) OS with or without vitamin D (median OS: 11.7 vs. 11.3 months, log-rank $p = 0.919$)

TABLE 3 Multivariate Cox proportional hazards model for time-to-treatment failure (TTF) and overall survival (OS)

Characteristic	TTF			OS		
	HR	95% CI	p-value	HR	95% CI	p-value
ECOG PS						
0 or 1	0.67	0.46–0.96	0.027	0.51	0.36–0.74	<0.001
2, 3 or 4						
Histology						
Squamous				1.52	1.10–2.10	0.012
Nonsquamous						
EGFR mutation						
Yes						
No	1.20	0.80–1.78	0.376			
Line of chemotherapy						
1	0.65	0.42–0.99	0.043	0.68	0.41–1.12	0.129
2	0.77	0.58–1.02	0.066	0.77	0.56–1.05	0.092
≧3						
Use of statins						
Yes	1.53	0.99–2.37	0.057			
No						
Use of antibiotics						
Yes	1.47	0.80–2.70	0.210			
No						
Use of NSAIDs						
Yes	1.01	0.76–1.35	0.930	1.08	0.78–1.50	0.627
No						
Use of PPIs						
Yes	1.17	0.87–1.57	0.299	1.36	0.96–1.91	0.081
No						
Use of opioids						
Yes	1.39	1.05–1.85	0.021	1.54	1.12–2.11	0.007
No						
Use of laxatives						
Yes	1.01	0.75–1.36	0.961	1.14	0.82–1.58	0.450
No						

Abbreviations: CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EGFR, epidermal growth factor receptor; HR, hazard ratio; NSAIDs, nonsteroidal anti-inflammatory drugs; PPIs, proton pump inhibitors.

clinical data were excluded, and the data of the remaining 300 patients were analyzed. The patient characteristics are summarized in Table 1. Among these patients, 189 (63.0%) had adenocarcinoma, 54 (18.0%) had ECOG PS ≥2, and 250 (83.3%) were current or former smokers. The PD-L1 expression status of 163 patients (54.3%) was unknown. The median line of chemotherapy was 2 (range: 1–11 lines). Medications used concomitantly at the beginning of nivolumab or pembrolizumab therapy are detailed in Table 1 and Table S1. In all, 254 patients (84.7%) used concomitant medications. The most frequently used concomitant medications included PPIs in 163 patients (54.3%), NSAIDs in 140 patients (46.7%), opioids in 114 patients (38.0%), and laxatives in 101 patients (33.7%).

TABLE 4 Immune-related adverse event (irAE)-types in patients treated with nivolumab or pembrolizumab

irAEs (*n* = 137)	All grade n	≥grade 3 n
Pneumonitis	31	13
Colitis (including diarrhea)	20	7
Skin toxicities	63	6
Thyroid dysfunction	27	0
Adrenal insufficiency/hypophysitis	10	8
Diabetes	3	3
Musculoskeletal (e.g., myalgia and arthralgia)	4	0
Hepatitis	5	1
Renal toxicities	1	0
Other	15	2

TABLE 5 Univariate and multivariate analyses of variable factors of immune-related adverse events (irAEs)

Characteristic	irAE (%)	Univariate analysis			Multivariate analysis		
		OR	95% CI	p-value	OR	95% CI	p-value
Age, years							
≧70	51.7						
<70	43.1	0.71	0.43–1.17	0.174	1.42	0.85–2.39	0.184
Sex							
Male	49.1						
Female	35.1	0.56	0.33–0.97	0.036	1.70	0.83–3.47	0.148
ECOG PS							
0 or 1	50.4	3.21	1.64–6.28	<0.001	0.31	0.16–0.62	0.001
2, 3, or 4	24.1						
Histology							
Squamous	43.2	0.88	0.52–1.49	0.630			
Nonsquamous	46.5						
EGFR mutation							
Yes	41.7	0.83	0.41–1.68	0.608			
No	46.2						
Line of chemotherapy							
1	50.0						
2	48.4						
≧3	42.0			0.498			
Smoking status							
Current or former	47.6	1.62	0.86–3.03	0.133	0.98	0.43–2.26	0.967
Never	36.0						
History of radiotherapy							
Yes	47.4	1.16	0.74–1.83	0.522			
No	43.8						
Use of statins							
Yes	46.2	1.02	0.46–2.29	0.958			
No	45.6						
Use of fibrates							
Yes	100			0.094[a]			
No	45.1						
Use of DPP-4							
Yes	40.9	0.81	0.34–1.96	0.642			
No	46.0						
Use of metformin							
Yes	62.5	2.02	0.47–8.61	0.476[a]			
No	45.2						
Use of ARBs							
Yes	42.5	0.86	0.44–1.69	0.666			
No	46.2						
Use of corticosteroids							
Yes	33.3	0.58	0.17–1.98	0.381			
No	46.2						
Use of antibiotics							
Yes	50.0	1.20	0.41–3.51	0.739			
No	45.5						

(Continues)

TABLE 5 (Continued)

Characteristic	irAE (%)	Univariate analysis			Multivariate analysis		
		OR	95% CI	p-value	OR	95% CI	p-value
Use of probiotics							
Yes	28.6	0.46	0.14–1.50	0.188	2.05	0.61–6.88	0.244
No	46.5						
Use of NSAIDs							
Yes	45.0	0.95	0.60–1.50	0.828			
No	46.3						
Use of PPIs							
Yes	42.9	0.79	0.50–1.24	0.302			
No	48.9						
Use of opioids							
Yes	42.1	0.79	0.50–1.27	0.332			
No	47.8						
Use of laxatives							
Yes	47.5	1.12	0.69–1.81	0.645			
No	44.7						
Use of vitamin D							
Yes	44.8	0.96	0.54–1.71	0.886			
No	45.9						

Abbreviations: ARBs, angiotensin receptor blockers; CI, confidence interval; DPP-4, dipeptidyl peptidase-4; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EGFR, epidermal growth factor receptor; NSAIDs, nonsteroidal anti-inflammatory drugs; OR, odds ratio; PPIs, proton pump inhibitors.
[a]Fisher's exact test.

Efficacy

Of the 300 patients, five achieved CR, 65 achieved PR, 65 achieved stable disease (SD), and 119 developed progressive disease (PD) according to RECIST v1.1.[25] Response was not evaluated in 46 patients due to early death or failure to follow-up. The overall response rate of patients treated with nivolumab or pembrolizumab was 23.3% (95% confidence interval [CI]: 18.9–28.4%). In the univariate analysis, there was a significant difference in the response rate with respect to the use of laxatives (odds ratio [OR] 0.51; 95% CI: 0.27–0.94, $p = 0.029$). Non-squamous histology (OR 3.17; 95% CI: 1.43–7.05, $p = 0.005$) and first- or second-lines of chemotherapy (first-line OR 3.91; 95% CI: 1.71–8.94, $p = 0.001$, second-line OR 1.97; 95% CI: 1.03–3.77, $p = 0.040$) were independently associated with better responses (Table 2).

The median TTF and OS in all patients treated with nivolumab or pembrolizumab were 2.5 months (95% CI: 1.8–3.2) and 11.7 months (95% CI: 9.0–14.4), respectively. The TTF and OS, with respect to the use of concomitant medications, are presented in Figures 1 and 2. The median OS was shorter in patients who used NSAIDs (8.8 vs. 15.9 months, $p = 0.014$). The median TTF and OS were shorter in patients who used PPIs (1.9 vs. 3.5 months, $p = 0.018$; 7.9 vs. 19.6 months, $p < 0.001$, respectively). The median TTF and OS were shorter in patients who used opioids (1.8 vs. 3.5 months, $p = 0.003$; 5.7 vs. 15.9 months,

$p < 0.001$, respectively). The median TTF and OS were shorter in patients who used laxatives (1.6 vs. 3.2 months, $p = 0.023$; 5.6 vs. 17.3 months, $p = 0.001$, respectively). Multivariate analysis for TTF showed that higher ECOG PS (hazard ratio [HR] 0.67; 95% CI: 0.46–0.96, $p = 0.027$), later lines of chemotherapy (first line HR 0.65; 95% CI: 0.42–0.99, $p = 0.043$), and opioid use (HR 1.39; 95% CI: 1.05–1.85, $p = 0.021$) were independently associated with shorter TTF. Multivariate analysis for OS showed that higher ECOG PS (HR 0.51; 95% CI: 0.36–0.74, $p < 0.001$), squamous histology (HR 1.52; 95% CI: 1.10–2.10, $p = 0.012$), and the use of opioids (HR 1.54; 95% CI: 1.12–2.11, $p = 0.007$) were independently associated with shorter OS (Table 3).

Safety

The proportion of patients who experienced irAEs was 45.7% ($n = 137$), among whom 32 (10.7%) had two or more irAEs. The most frequent irAEs were skin toxicities ($n = 63$), including rash, pruritus, and erythema multiforme, pneumonitis ($n = 31$), and thyroid dysfunction ($n = 27$). A total of 38 patients (12.7%) experienced irAEs of grade 3 or higher (Table 4). In the univariate analysis, there was no significant difference in the incidence of irAEs with respect to the use of concomitant medications. All three patients who used fibrates experienced irAEs, but the

OR could not be calculated. Therefore, the p-value for the use of fibrates was <0.2, but it was not included in the multivariate analysis. In the multivariate analysis, only ECOG PS was an independent factor (OR 0.31; 95% CI: 0.16–0.62, $p = 0.001$) (Table 5).

DISCUSSION

In the present study, the impact of concomitant medication use on the efficacy and safety of immune checkpoint inhibitors was evaluated. The overall response rate, median TTF, and OS found in this study were consistent with those reported in previous studies.[3,6,7,11,15,27] In our study, patients with NSCLC of nonsquamous histology had a significantly higher response rate than those with NSCLC of squamous histology. The overall response rate for the first line was significantly higher than that for second or later lines. These results are consistent with the findings of previous studies.[28,29] In our study, the TTF and OS of patients treated with ICIs as the first or second line tended to be better than those treated with ICIs as the third line or higher, which is in agreement with a previous report.[29] Consistent with existing reports, nonsquamous histology was independently associated with better OS than squamous histology.[5] ECOG PS was independently associated with the shortening of TTF or OS, which is consistent with existing reports.[5,6,30]

The proportion of patients who experienced irAEs in the present study was similar to that reported in a previous study.[24] However, in contrast to previous studies, the incidence of irAEs was significantly lower in patients with an ECOG PS of 2 or higher.[31,32] This may be explained by the fact that the median TTF (1.0 month) (95% CI: 0.8–1.2) was significantly shorter in patients with an ECOG PS of 2 or higher. It has been previously reported that there was no difference in the incidence of irAEs with or without metformin intake,[16,17] and our study revealed that use of other concomitant medications had no significant effect on irAEs. The expression of IFN-γ mRNA was previously shown to be upregulated in vivo following bezafibrate administration plus PD-1 blockage[33]; thus, the incidence of irAEs might increase with fibrate use. In our study, all three patients who used fibrates experienced irAEs, but a larger sample size should be used in the future to examine the relationship between the intake of fibrates and irAEs more thoroughly.

To our knowledge, this is the first study to demonstrate no association between ARBs or vitamin D and the efficacy and safety of nivolumab or pembrolizumab in patients with NSCLC. Notably, for the first time, we found that there was no significant difference in the incidence of irAEs in patients treated with nivolumab or pembrolizumab for NSCLC with or without the use of concomitant medications, excluding metformin. However, our study had several limitations; this was a retrospective study conducted at a single center. Patient adherence and the duration of use of medications with immunomodulatory effects, as well as patient history of noncancerous diseases, were unknown. A small number

of patients were treated with concomitant medications. Other factors that may affect the efficacy of ICIs, such as site of metastasis[34] and PD-L1 expression,[35] were not considered. In addition, irAEs were not evaluated based on whether steroids were needed.

Although the use of opioids was an independent factor for TTF and OS, data from this retrospective analysis indicate that the clinical outcomes of patients treated with nivolumab or pembrolizumab for NSCLC were not significantly different with or without concomitant medication. The results obtained for each concomitant medication are discussed below.

Statin use was found to be associated with better responses or longer TTF in patients treated with nivolumab for advanced NSCLC.[11] In this study, the use of statins was limited to 10 cases. However, in another study in which statins were used concomitantly in 13.8% or 26.5% of patients, there were no significant differences in response, PFS, and OS.[15,36] It has been reported that the depletion of membrane cholesterol may lead to immunosuppression[37]; however, in other studies including this study, cholesterol levels were unknown. In the future, the influence of statins and cholesterol status on the efficacy of ICIs in a larger number of patients, should be evaluated.

As in this study, the impact of metformin on the efficacy of ICIs has only been assessed in relatively small groups of patients.[15–17,36] The results of clinical trials currently in progress, which consider the concomitant use of metformin and nivolumab, are expected in the future.[38,39]

Although the number of patients who used fibrates in this study was small, fibrate use had no significant effect on the efficacy of ICIs, as previously reported.[11,15]

Similar to the findings of a previous study,[11] there was no significant difference in the efficacy of ICIs with or without concomitant use of DPP-4 inhibitors. The in vivo synergistic effects of DPP-4 inhibitors were observed previously in combination with cytotoxic T-lymphocyte-associated protein 4 inhibitors, but not with PD-1 inhibitors.[19] Therefore, the impact of DPP-4 inhibitors may be different in patients treated with PD-L1 inhibitors.

ARBs previously showed in vivo synergistic effects with PD-L1 antibody treatment by reducing the production of various immunosuppressive cytokines.[20] However, in this study, it was clarified for the first time that the use of ARBs does not affect the efficacy of ICIs in patients with NSCLC. The impact of ARBs on the tumor microenvironment in mouse colorectal cancer models has been previously reported.[20,40] The impact of ARBs on the immune response may differ depending on the cancer type. Furthermore, the ARB used in mouse models was valsartan at a dose of 15 mg/kg,[20] which is higher than the normal dose in humans. This difference in dose may have affected the results of the mouse study.

Use of corticosteroids at a dose ≥10 mg prednisone-equivalent was previously associated with poorer outcomes in patients treated with PD-1 inhibitors for NSCLC.[9,36] The impact of corticosteroids on the efficacy of ICIs was probably not observed in our study because the corticosteroid

dose used was less than 10 mg prednisone-equivalent in most patients.

The overall response was significantly different in patients who had used antibiotics within 30 days prior to the start of treatment with ICIs, than in patients who had used antibiotics concurrently with ICIs, as previously reported.[8,36] In contrast, PFS and OS were previously lower in patients with higher ratios of "days under antibiotics/days under ICIs".[13] The duration of antibiotic use may have influenced the results of our study.

Although the number of patients who used probiotics in this study was small, as previously reported, probiotic use had no significant effect on the efficacy of ICIs.[15]

The overall response and OS in patients treated with ICIs for NSCLC were not significantly different from those obtained in a previous study.[15] However, unlike in our study, the PFS in patients who used NSAIDs one month before and after starting treatment with nivolumab was significantly longer in the multivariate analysis of the previous study. [15] These contradictory findings may be due to the fact that NSAIDs were only used in our study during ICI initiation. In addition, the use of opioids was not considered in the previous study. A total of 70 patients (50.0%) concomitantly used NSAIDs and opioids, and this might have led to bias in the results of our study.

In previous studies, the OS of patients who used PPIs was significantly shorter in the ICI group in the chemotherapy group.[12,36] A total of 79 patients (48.5%) used PPIs concomitantly with opioids, and this might have led to bias in the results of our study, as opioid use was not considered in previous studies. The effects of PPIs on the biological processes of the gut microbiota as well as on the efficacy of ICIs should be clarified through further research.

Opioids affect immune cells via direct interactions with immune cells expressing opioid receptors or via indirect immunosuppressive effects, for example, through the sympathetic nervous system and the hypothalamic–pituitary–adrenal axis.[41] In this study, the overall response was not significantly different with or without the use of opioids, but TTF and OS were significantly shortened in patients who had used opioids, as previously reported.[13] Opioids are used for the treatment of pain associated with disease progression, and as such, the shortened TTF or OS of patients using opioids may reflect this progression. Further research is needed to determine whether use of opioids is purely a poor prognostic factor or a factor that directly affects the efficacy of ICIs.

Disease control rates have been reported to be previously lower in NSCLC patients with stool abnormalities than in those without stool abnormalities.[27] In future, the effects of laxatives as well as bowel movements on ICI treatment outcomes should be examined. In addition, 65 patients (64.4%) used laxatives concomitantly with opioids, which was an independent factor for TTF and OS in our study.

Vitamin D deficiency has been associated with poor survival in melanoma patients. The impact of vitamin D supplementation in clinical trials remains controversial.

Recently, it was suggested that vitamin D works synergistically with ICIs due to its immunomodulatory effects and associated upregulation of PD-L1 expression.[14] In our study, for the first time, the efficacy of ICIs in patients with NSCLC was found not to be significantly different with or without the use of vitamin D. However, vitamin D plasma levels were not measured in our study. Therefore, in future, the impact of vitamin D on ICI treatment as well as vitamin D plasma levels should be examined.

In conclusion, in this study, the efficacy and safety of nivolumab or pembrolizumab in the treatment of advanced NSCLC were not significantly different with or without concomitant medication. Our results suggest that use of opioids might be associated with shorter OS in patients treated with ICIs. Whether use of opioids is purely prognostic or contributes to resistance to ICIs remains unclear. The impact of concomitant medications on the clinical outcomes of ICI treatment should be clarified through further studies, by elucidating the underlying biological mechanisms.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.