Journal of Infection and Chemotherapy 29 (2023) 1038–1045

Contents lists available at ScienceDirect

Journal of Infection and Chemotherapy

journal homepage: www.elsevier.com/locate/jic

Original Article

Immunogenicity and safety of influenza vaccine in patients with lung cancer receiving immune checkpoint inhibitors: A single-center prospective cohort study

Kei Nakashima [a,b,e,*], Yuya Homma [a], Jumpei Taniguchi [a], Norihiko Kubota [a], Ayumu Otsuki [a], Hiroyuki Ito [a], Yoshihito Otsuka [c], Kyoko Kondo [d], Satoko Ohfuji [e,f], Wakaba Fukushima [e,f], Yoshio Hirota [g]

[a] Department of Pulmonology, Kameda Medical Center, 929 Higashi-cho, Kamogawa, Chiba, 296-8602, Japan
[b] Kameda Institute for Health sciences, 462 Yokosuka, Kamogawa, Chiba, 296-0001, Japan
[c] Department of Clinical Laboratory, Kameda Medical Center, 929 Higashi-cho, Kamogawa, Chiba, 296-0041, Japan
[d] Management Bureau, Osaka Metropolitan University Hospital, 1 Chome-5-7 Asahimachi, Osaka, 545-0051, Japan
[e] Department of Public Health, Graduate School of Medicine, Osaka Metropolitan University, 1 Chome-4-3 Asahimachi, Osaka, 545-8585, Japan
[f] Research Center for Infectious Disease Sciences, Graduate School of Medicine, Osaka Metropolitan University, 1 Chome-4-3 Asahimachi, Osaka, 545-8585, Japan
[g] Clinical Epidemiology Research Center, SOUSEIKAI Medical Group (Medical Co. LTA), 3-5-1 Kashiiteriha, Higashi-ku, Fukuoka, 813-0017, Japan

ARTICLE INFO

Keywords:
Influenza vaccine
Immune checkpoint inhibitor
Immunogenicity
Lung cancer
Safety

ABSTRACT

Introduction: Patients with lung cancer have a high risk of influenza complications. International guidelines recommend annual influenza vaccination for patients with cancer. Immune checkpoint inhibitors (ICIs) are progressively used to treat lung cancer. Data regarding immunogenicity and safety of influenza vaccine are limited in patients with lung cancer receiving ICIs; therefore, we conducted this single-center, prospective observational study in the Japanese population.

Methods: Patients with lung cancer receiving ICIs and influenza immunization were enrolled. Blood samples were collected from patients for serum antibody titer measurement pre- and 4 ± 1 weeks post-vaccination. The primary endpoint was seroprotection rate (sP) at 4 ± 1 weeks post-vaccination. The secondary endpoints were geometric mean titer (GMT), mean fold rise, seroresponse rate (sR), seroconversion rate (sC), and immune-related adverse events (irAEs), defined as adverse effects caused by ICI administration, 6 months post-vaccination.

Results: Influenza vaccination in the 23 patients included in the immunogenicity analyses significantly increased GMT for all strains, and sP, sR, and sC were 52%–91%, 26%–39%, and 26%–35%, respectively. In the 24 patients included in the safety analyses, 7 (29%) and 5 (21%) patients exhibited systemic and local reactions, respectively. Only one patient (4%) (hypothyroidism, grade 2) showed post-vaccination irAEs.

Conclusions: Overall, influenza vaccination in patients with lung cancer receiving ICIs showed acceptable immunogenicity and safety, thus supporting annual influenza vaccination in this population.

1. Introduction

Lung cancer is the leading cause of cancer-related deaths, accounting for 1.8 million deaths worldwide in 2020 [1]. Chemotherapy is the mainstay of treatment for patients with advanced lung cancer, and the development of therapeutic agents has progressed over the years. In addition to cytotoxic drugs, molecular-targeted drugs have emerged, and prognosis has improved [2]. Recently, the development of immune checkpoint inhibitors (ICIs), including programmed death receptor-1 (PD-1) and programmed cell death 1-ligand 1 (PD-L1) inhibitors, has

Abbreviations: ACTH, adrenocorticotropic hormone; GMT, geometric mean titer; HA, hemagglutinin; HI, hemagglutination inhibition; ICIs, immune checkpoint inhibitors; IQR, interquartile range; irAEs, immune-related adverse events; MFR, mean fold rise; NOS, not otherwise specified; PD-1, programmed death receptor-1; PD-L1, programmed cell death 1-ligand 1; sC, seroconversion rate; sR, seroresponse rate.

* Corresponding author. Department of Pulmonology, Kameda Medical Center, 929 Higashi-cho, Kamogawa, Chiba, 296-8602, Japan.
E-mail address: kei.7.nakashima@gmail.com (K. Nakashima).

https://doi.org/10.1016/j.jiac.2023.07.008
Received 27 March 2023; Received in revised form 27 June 2023; Accepted 19 July 2023
Available online 20 July 2023

improved the prognosis of lung cancer, and they are increasingly used in clinical practice following international guidelines [3]. PD-1 and PD-L1 promote tumor cell evasion during the host immune attack, and ICIs exert their antitumor effects by inhibiting them [4]. In the non-small cell lung cancer treatment, pembrolizumab, atezolizumab, and nivolumab plus ipilimumab are the first-line drugs of choice according to the PD-L1 tumor proportion score [3,5–7]. Combinations of cytotoxic agents and ICIs are also used in first-line therapy for lung cancer [3,8,9].

Patients with cancer represent a high-risk population for influenza virus infection, leading to complications, treatment delays, and even death [10,11]. Thus, international guidelines recommend annual influenza vaccination for these patients [12,13]. A previous study showed that influenza vaccine immunogenicity was acceptable in patients with lung cancer who were receiving cytotoxic agents [14]. In addition, a Cochrane meta-analysis reported that influenza vaccination in patients with cancer resulted in lower mortality and influenza-related outcomes [15]. However, no study has evaluated the immunogenicity and safety of influenza vaccines, specifically in patients with lung cancer receiving ICIs [16–18]. Therefore, in this single-center prospective study, we evaluated the immunogenicity and safety of quadrivalent influenza vaccines in patients to support the influenza vaccination recommendations.

2. Patients and methods

2.1. Study participants

In this prospective cohort study, patients with lung cancer who were receiving ICI treatment at the Department of Pulmonary Medicine, Kameda Medical Center, Chiba, Japan, were invited to participate in the study in November and December 2020. The following patients were included: patients with lung cancer aged 50 years or older and who were receiving ICIs, patients willing to receive influenza vaccination voluntarily, and patients who provided written consent to participate in this study. The following patients were excluded: patients who had already received influenza vaccine for the 2020/2021 season, patients who had experienced anaphylaxis or were at a risk of anaphylaxis due to influenza vaccine components, patients allergic to eggs, individuals already diagnosed with influenza in the 2020/2021 season, patients who had an acute febrile illness or other serious illnesses at the time of vaccination, patients who received cytotoxic anticancer drugs within 1 month of vaccination, patients receiving steroids or immunosuppressive drugs (excluding those administered as antiemetics), and any other patient who had an unsuitable condition for vaccination. A total of 24 patients with lung cancer were registered for this study. The protocol complied with the Helsinki Declaration of 1975 and was approved by the Research Ethics Committee of Kameda Medical Center (#20-064-200923). Written informed consent was obtained from all enrolled participants. In addition, this study was registered with the University Hospital Medical Information Network (UMIN 000041923).

We collected the following data of patients' characteristics from the Kameda Medical Center medical records: age at enrollment, sex, body mass index, influenza vaccination in the previous year, Eastern Cooperative Oncology Group performance status, smoking history, lung cancer histology, tumor stage, ICI type (pembrolizumab, atezolizumab, durvalumab, or nivolumab), number of ICI treatment cycles, and immune-related adverse effects (irAEs) pre-vaccination.

2.2. Primary and secondary endpoints

The primary endpoint was the seroprotection rate (sP) (proportion of hemagglutination inhibition (HI) antibody titer of 1:40 or higher) at 4 ± 1 weeks (21–35 days) post-vaccination (S1). The secondary endpoints were geometric mean titer (GMT) at pre-vaccination (S0) and S1 and mean fold rise (MFR), seroresponse rate (sR) (proportion of HI antibody titer of four times or higher) and seroconversion rate (sC) (pre-vaccination HI antibody titer <1:10 and post-vaccination HI antibody titer ≥1:40, pre-vaccination antibody titer ≥1:10 and post-vaccination HI antibody titer ≥4-fold) at S1, and irAEs at 6 months post-vaccination.

2.3. Influenza vaccination

An inactivated quadrivalent influenza hemagglutinin (HA) vaccine was used (2020/2021 season) (FLUBIK HA Syringes® manufactured by the Research Foundation for Microbial Diseases of Osaka University). The vaccine strains were as follows: A/Guangdong-Maonan/SWL 1536/2019 (CNIC-1909) (A[H1N1]pdm09, hereafter referred to as H1N1), A/Hong Kong/2671/2019 (NIB-121) (H3N2), B/Phuket/3073/2013 (Yamagata lineage), and B/Victoria/705/2018 (BVR-11) (Victoria lineage). Each vaccine contained more than 15 μg HA antigen of each strain. A single subcutaneous inoculation of 0.5 mL of the vaccine, the typical administration route used in Japan, was employed. The ICI administration and influenza vaccination were planned to be performed on the same day.

2.4. Measurement of antibody titers

Serum samples were collected at S0 and S1. All serum specimens were stored at −20 °C in the Kameda Medical Center laboratory before analysis. Serum antibody levels to HA were measured following a standard microtiter hemagglutination inhibition method with the same antigens used in the vaccine [19]. All samples were assayed at the Research Foundation for Microbial Diseases of Osaka University, Osaka, Japan, in March 2021.

2.5. Safety

Local reactions at the injection site and systemic reactions were monitored for 14 days using case cards completed by the participants. The local reactions were evaluated as redness, swelling, induration, itching, and pain in the injection site. Systemic reactions were evaluated as fever (temperature ≥37.5 °C), fatigue, arthralgia or myalgia, headache, and rash. Grades of erythema, swelling, and induration were defined as follows: grade 1 within a few centimeters, grade 2 from the elbow to the shoulder, and grade 3 extending beyond the elbow. Fever was defined as grade 1 at 37.5–38.4 °C, grade 2 at 38.5–39.4 °C, and grade 3 at 39.5 °C or higher. For itching, pain, fatigue, arthralgia, myalgia, and headache, grade 1 was defined as not bothersome, grade 2 as bothersome but tolerable, and grade 3 as not tolerable. A rash was defined as grade 1 if limited to the part of the body and grade 2 if present all over the body.

2.6. Follow-up survey

For study subjects, influenza diagnosis and the presence of influenza-like illness (defined by acute febrile illness [temperature >38.0 °C] with one or more respiratory symptoms [nasal discharge, sore throat, or cough]) were investigated using a questionnaire. In addition, the presence or absence of irAEs, defined as adverse effects caused by the administration of ICIs, at 6 months post-vaccination was evaluated using the medical records at the Kameda Medical Center [20].

2.7. Statistical analysis

Based on previous studies, we hypothesized that patients with lung cancer who are receiving ICIs have 85% sP against A(H3N2) at 1 month post-vaccination [14,17,21–23]. The U.S. Food and Drug Administration (FDA) has established criteria for evaluating influenza vaccine immunogenicity in individuals older than 65 years. The criteria specify that the lower bound of the two-sided 95% confidence interval (CI) for the percentage of participants achieving an HI antibody titer of ≥1:40 should meet or exceed 60% [24]. Following the criteria, we calculated

the number of cases required to maintain the confidence interval of the sP within 30%, aiming for a lower limit of 95% CI of the sP exceeding 60%. Based on this calculation, 22 patients were required for immunogenicity analysis. Assuming a 15% dropout rate, the target number of enrollment patients was set to 25.

Patients with influenza-like symptoms or infections by blood collection at S1 were excluded because the purpose of this study was immunogenicity evaluation, not vaccine effectiveness. Immunogenicity of the influenza vaccine was based on GMT, MFR, sP, sR, and sC. If HI antibody titer <1:10, the value was replaced by 5. The frequency (percentage) of systemic or local reactions was assessed over 14 days for safety analysis. In addition, we calculated irAE frequency for 6 months post-vaccination. The significance of an increase in antibody levels within groups was assessed using the Wilcoxon signed-rank test, and comparisons between the groups were made using the Wilcoxon rank-sum or Kruskal–Wallis test. The Student's *t*-test along with Fisher's exact, Jonckheere–Terpstra, and Cochran–Armitage tests were performed where appropriate. Results with a p-value <0.05 were considered significant. All analyses were performed using R (R Foundation for Statistical Computing).

3. Results

All patients received one dose of the quadrivalent influenza vaccine between November and December 2021. Influenza vaccination was performed on the same day as the ICI administration, except for one patient who received the influenza vaccine 21 days after and 7 days before the regular ICI administration. One patient received steroids for radiation pneumonitis treatment before the collection of serum samples at S1. Thus, serum samples at 4–6 weeks post-vaccination were collected from 23 patients with lung cancer, exceeding the pre-required sample size of 22 cases for immunogenicity analysis. All 24 patients were evaluated for safety analyses. During the study period, no subject reported laboratory-confirmed influenza or influenza-like illness.

The characteristics of the 23 patients included in the immunogenicity analyses are shown in Table 1. Their median age was 71 years, and 22 of the patients (96.0%) were men. Fifteen patients (65%) received influenza vaccination in the 2019/2020 season. The median body mass index (kg/m^2) was 22.4. Adenocarcinoma was the most common histological type of lung cancer (48%). Pembrolizumab, atezolizumab, and durvalumab were administered to 10 (44%), 7 (30%), and 5 (22%) patients, respectively, whereas nivolumab was administered to 1 (4%) patient.

Immune responses to the influenza vaccine in patients with lung cancer receiving treatment with ICIs are shown in Table 2. The MFR was 3.5 for A(H1N1) ($p < 0.001$), 3.3 for A(H3N2) ($p = 0.001$), 2.5 for B (Yamagata) ($p < 0.001$), and 3.2 for B(Victoria) ($p < 0.001$); significant increases were observed in the MFR for all four strains. Regarding the primary endpoint, the sP was 65% for A(H1N1), 91% for A(N3N2), 70% for B(Yamagata), and 52% for B(Victoria). For A(H3N2), the sP was 91% (95% CI, 72%–99%), as we hypothesized, and the lower 95% CI limit exceeded 60%, meeting the FDA criteria for the elderly population [24]. The sR and sC were 26%–39% and 26%–35%, respectively.

Table 3 shows the comparison between our study and a previous study that assessed the immunogenicity of the quadrivalent influenza vaccine in healthy Japanese individuals [25]. The table also includes the FDA and European Medicines Agency (EMA) criteria for assessing the immunogenicity of influenza vaccines [24,26]. The previous study involved 78 healthy adults aged 20 years and above, with a mean age of 37.8 years [25]; the MFR was 1.3–6.6, sP was 29.5%–98.7%, and sC was 2.6%–76.9%. In our study, the MFR was 2.5–3.5, sP was 52.2%–91.3%, and sC was 26.1%–34.8%, and a straightforward comparison between the studies is difficult due to differences in the survey seasons. Nevertheless, regarding the B/Phuket/3073/2013 (Yamagata) strain, which is identical in both this study and the previous study, the sP was 69.6% in this study and 67.9% in the previous study, suggesting comparable immunogenicity. When the immunogenicity determined in this study was evaluated according to the FDA criteria, the A(H3N2) strain met the FDA criteria (sP's lower limit of 95% CI was 72.0% $\geq$ 60%), whereas the other strains did not. Furthermore, when evaluated based on the EMA criteria, the MFR for all strains exceeded 2.0; except B(Victoria), all strains met sP > 60%; and except B(Yamagata), all strains met sC > 30%. Therefore, it can be concluded that all strains meet the EMA criteria.

Table 1
Characteristics of the patients with lung cancer included in the immunogenicity analyses.

Characteristic	Patient (N = 23)
Age median (IQR) (years)	71 (66.5–76.5)
Male	22 (96)
BMI (kg/m^2) median (IQR)	22.4 (20.6–25.9)
Influenza vaccination in last year	15 (65)
Eastern Cooperative Oncology Group performance status	
0	20 (87)
1	3 (13)
Smoking	
Non-smoker	1 (4)
Ex-smoker	20 (87)
Current smoker	2 (9)
Histological type	
Adenocarcinoma	11 (48)
Squamous cell carcinoma	8 (35)
Small cell carcinoma	2 (9)
NOS	1 (4)
Pleomorphic carcinoma	1 (4)
Tumor stage	
II	1 (4)
III	6 (26)
IV	4 (17)
Recurrence after chemoradiotherapy	2 (9)
Recurrence after stereotactic Radiotherapy and cryotherapy	2 (9)
Recurrence after surgery	8 (35)
Immune checkpoint inhibitor	
Pembrolizumab	10 (44)
Atezolizumab	7 (30)
Durvalumab	5 (22)
Nivolumab	1 (4)
Number of cycles of immune checkpoint inhibitor treatment	
1–5	7 (30)
6–10	7 (30)
11–15	2 (9)
16–20	4 (17)
21–25	2 (9)
≥26	1 (4)
Number of immune-related adverse effects pre-vaccination	
Total	3 (13)
Rash	1 (4)
Isolated ACTH deficiency	1 (4)
Hypothyroidism	1 (4)

Data are expressed as n (%) of patients, unless otherwise indicated.
IQR, interquartile range; BMI, body mass index; NOS, not otherwise specified; ACTH, adrenocorticotropic hormone.

The immunogenicity of the influenza vaccine for the A(H1N1) strain is shown in Table 4. No significant differences were observed in GMT at S1 and MFR, stratified by age and ICI regimens. However, the MFR tended to be higher in patients with lower pre-vaccination antibody titers, whereas the sP tended to be higher in patients with higher pre-vaccination antibody titers. On the contrary, the sR and sC tended to be higher in patients with lower pre-vaccination antibody titers.

The immunogenicity of the influenza vaccine for the A(H3N2) strain is shown in Table 5. No differences were observed in the GMT at S1 and MFR, stratified by age and ICI regimens. The MFR was significantly higher at lower pre-vaccination antibody titers. The sP was significantly higher at higher pre-vaccination antibody titers. The sR and sC were significantly higher at lower pre-vaccination antibody titers.

The immunogenicity of the influenza vaccine for the B(Yamagata) strain is shown in Table 6. In the age-stratified analyses, the GMT at S1 and MFR were significantly higher in patients aged <70 years than in

Table 2
Immune response to influenza vaccines in patients with lung cancer receiving immune checkpoint inhibitor treatment (n = 23).

	Geometric mean titer		Mean fold rise (S1/S0)	Post-vaccination		
	Pre-vaccination (S0)	Post-vaccination (S1)		Seroprotection rate (sP) (1 ≥ 1:40): n (%)	Seroresponse rate (sR) (≥4-fold-rise): n (%)	Seroconversion rate (sC) n (%)
A(H1N1)	11	35	3.5 ($p < 0.001$)	15 (65)	8 (35)	8 (35)
A(H3N2)	21	53	3.3 ($p = 0.001$)	21 (91)	9 (39)	8 (35)
B(Yamagata)	21	43	2.5 ($p < 0.001$)	16 (70)	6 (26)	6 (26)
B(Victoria)	10	30	3.2 ($p < 0.001$)	12 (52)	8 (35)	7 (30)

For statistical analysis, the Wilcoxon rank-sum test was performed. Results with $P < 0.05$ were considered significant.

Table 3
Comparison between our study and a previous study that assessed the immunogenicity of the quadrivalent influenza vaccine in healthy Japanese individuals, including the FDA and EMA's criteria for assessing the immunogenicity of influenza vaccines.

	Mean fold rise (S1/S0)	Post-vaccination	
		Seroprotection rate (sP) (1 ≥ 1:40): n (%)	Seroconversion rate (sC): n (%)
FDA criteria for adults ≥65 years of age (reference 24)[a]		≥60% (lower limit of 95% CI)	≥30% (lower limit of 95% CI)
EMA criteria for adults >60 years of age (reference 26)[b]	>2.0	>60%	>30%
Present study (23 patients with lung cancer receiving ICI, with a median age of 71 years)			
A/Guangdong-Maonan/SWL 1536/2019 (H1N1)	3.5	65.2 (42.7–83.6)	34.8 (16.4–57.3)
A/Hong Kong/2671/201 (H3N2)	3.3	91.3 (72.0–98.9)	34.8 (16.4–57.3)
B/Phuket/3073/2013 (Yamagata)	2.5	69.6 (47.1–86.8)	26.1 (10.2–48.4)
B/Victoria/705/2018 (Victoria)	3.2	52.2 (30.6–73.2)	30.4 (13.2–52.9)
Previous study (78 healthy individuals, with a mean age of 37.8 years) (reference 25)			
A/California/7/2009 (H1N1)	1.4	80.8 (72.0–89.5)	7.7 (1.8–13.6)
A/Switzerland/9715293/2013 (H3N2)	6.6	98.7 (96.2–100.0)	76.9 (67.6–86.3)
B/Phuket/3073/2013 (Yamagata)	1.4	67.9 (57.6–81.6)	2.6 (0.9–6.1)
B/Texas/2/2013 (Victoria)	1.3	29.5 (19.4–39.6)	3.9 (0.4–8.1)

CI, confidence interval; EMA, European Medicines Agency; HI, HI, hemagglutination inhibition; FDA, Food and Drug Administration.

[a] FDA criteria For adults ≥65 years of age:1) The lower bound of the two-sided 95% CI for the percent of participants achieving seroconversion for HI antibody should meet or exceed 30%.2) The lower bound of the two-sided 95% CI for the percent of participants achieving an HI antibody titer of ≥1:40 should meet or exceed 60%.

[b] EMA criteria: the following serological assessments should be considered for each strain in adult individuals aged over 60 years, and at least one of the assessments should meet the indicated criteria.1) number of seroconversions or significant increase in anti-hemagglutinin antibody titer >30%. 2) mean geometric increase >2.0. 3) the proportion of participants achieving HI titer ≥40 should be >60%.

those aged ≥70 years. In the ICI regimen-stratified analyses, no significant differences were observed in the GMT at S1 and MFR. The sP tended to be higher for pre-vaccination titers ≥1:40.

The immunogenicity of the influenza vaccine for B(Victoria) is shown in Table 7. No significant differences were observed in the GMT at S1 and MFR, stratified by age and ICI regimens. The sR was significantly higher for lower pre-vaccination antibody titers.

The characteristics of the 24 patients included in the safety analyses are shown in Table S1. Adverse events in patients with lung cancer receiving treatment with ICIs are shown in Table 8. Systemic reactions were observed in seven patients (29%); all systemic reactions were of grades 1 and 2 and were resolved within a few days. Local reactions were observed in five patients (21%). Local reactions such as erythema, swelling, induration, and itching were all grade 1, and the pain was grades 1 and 2, all of which were resolved within 5 days. An irAE was observed in one patient (4%) (hypothyroidism, grade 2) within 6 months post-vaccination.

4. Discussion

In this study, influenza vaccination in patients with lung cancer who were receiving ICIs resulted in a significant increase in GMT for all strains. Regarding the primary endpoint, the sP was 52%–91%, the sP for A(H3N2) was 91% (95% CI, 72%–99%), and the lower 95% CI limit exceeded 60%, meeting the FDA criteria as we hypothesized [24]. The sR and sC were 26%–39% and 26%–35%, respectively. B/Phuket/3073/2013 (Yamagata) induced equivalent sP levels in this study and a previous study involving healthy individuals [25], suggesting similar immunogenicity. Although strains other than A(H3N2) did not meet the FDA criteria, all strains met the EMA criteria. Adverse reactions were mild and tolerable. Only one case (4%) (hypothyroidism, grade 2) of post-vaccination irAE was observed. Considering these results, we believe the study supports the administration of inactivated influenza vaccinations in patients with lung cancer who are undergoing ICI treatment, owing to its acceptable immunogenicity and safety.

A previous study has evaluated immunogenicity in patients with solid tumors receiving ICIs [16]. In a study conducted in Switzerland, the sP, after the administration of inactivated influenza virus vaccine, was 50%–77.8% in 23 patients with solid cancers who were receiving ICIs, with no difference compared with the sP in healthy subjects [21]. An observational study conducted in France during the 2018/2019 influenza season reported that the sP for A(H1N1) and A(H3N2), after influenza vaccination in patients with solid tumors (including 25 patients with lung cancer) who were receiving ICIs, was 63%–71% and 57%–67%, respectively [27]. Furthermore, a prospective study conducted at two Korean core hospitals reported that the sP and sC after seasonal influenza vaccination were higher in patients with lung cancer who were receiving ICIs (n = 46) than in patients with cancer who were receiving cytotoxic drugs (n = 90) [17]. In this study, the sP and sC of the ICI group were 76%–89% and 52%–65%, respectively, whereas the sP and sC of the cytotoxic chemotherapy group were 48%–70% and 27%–39%, respectively [17]. In the present study, influenza vaccination in patients with lung cancer who were receiving ICIs resulted in a significant increase in GMT for all strains, 52%–91% of sP, 26%–39% of sR, and 26%–35% of sC. The influenza vaccination coverage in the previous year was 65% for all patients in our study, and the proportion of pre-vaccination antibody titers ≥1:40 was high, with 4 (17%) cases for A(H1N1), 10 (43%) for A(H3N2), and 8 (35%) for B(Yamagata). This may have resulted in the higher sP with lower sR and sC in this study than the

Table 4
Immunogenicity of A(H1N1) strain influenza vaccine in patients with lung cancer receiving immune checkpoint inhibitor treatment.

		Geometric mean titer		Mean fold rise (S1/S0)	Post-vaccination		
	N	Pre-vaccination (S0)	Post-vaccination (S1)		Seroprotection rate (sP) (1 ≥ 1:40): n (%)	Seroresponse rate (sR) (≥4-fold-rise): n (%)	Seroconversion rate (sC)
Age (years)							
<70	11	12	54	4.3 ($p = 0.009$)	7 (64)	4 (36)	4 (36)
≥70	12	10	31	3.0 ($p = 0.011$)	8 (67)	4 (33)	4 (33)
		$p = 0.616$	$p = 0.365$	$p = 0.452$	$p = 1.000$	$p = 1.000$	$p = 1.000$
Sex							
Male	22	12	38	3 ($p < 0.001$)	14 (64)	7 (32)	7 (32)
Female	1	5	320	64 (NA)	1 (100)	1 (100)	1 (100)
		$p = 0.413$	$p = 0.146$	$p = 0.107$	$p = 1.000$	$p = 0.348$	$p = 0.348$
Pre-vaccination titer							
<1:10	12	5	25	5 ($p = 0.004$)	6 (50)	6 (50)	6 (50)
1:10–1:20	7	16	59	3.6 ($p = 0.015$)	5 (71)	2 (29)	2 (29)
≥1:40	4	80	95	1.2 ($p = 0.391$)	4 (100)	0 (0)	0 (0)
		$p < 0.001$	$p = 0.079$	$p = 0.095$	$p = 0.063$	$p = 0.063$	$p = 0.063$
Immune checkpoint inhibitor							
Pembrolizumab	10	9	46	5.3 ($p = 0.009$)	7 (70)	5 (50)	5 (50)
Atezolizumab	7	15	44	3 ($p = 0.025$)	4 (57)	2 (28.6)	2 (28.6)
Durvalumab	5	17	23	1.3 ($p = 0.178$)	3 (60)	0 (0)	0 (0)
Nivolumab	1	5	160	32 (NA)	1 (100)	1 (100)	1 (100)
		$p = 0.392$	$p = 0.599$	$p = 0.138$	$p = 0.910$	$p = 0.136$	$p = 0.136$

For statistical analysis, the Wilcoxon rank-sum test, Wilcoxon signed-rank test, Fisher's exact test, Kruskal–Wallis test, Jonckheere–Terpstra test, or Cochran–Armitage test was performed as appropriate. $P < 0.05$ was considered significant.
NA, not applicable.

Table 5
Immunogenicity of A(H3N2) strain influenza vaccine in patients with lung cancer receiving immune checkpoint inhibitor treatment.

		Geometric mean titer		Mean fold rise (S1/S0)	Post-vaccination		
	N	Pre-vaccination (S0)	Post-vaccination (S1)		Seroprotection rate (sP) (1 ≥ 1:40): n (%)	Seroresponse rate (sR) (≥4-fold-rise): n (%)	Seroconversion rate (sC)
Age (years)							
<70	11	21	66	3.1 ($p = 0.020$)	9 (82)	4 (36)	3 (27)
≥70	12	23	84	3.5 ($p = 0.006$)	12 (100)	5 (42)	5 (42)
		$p = 0.777$	$p = 0.678$	$p = 0.799$	$p = 0.217$	$p = 1.000$	$p = 0.667$
Sex							
Male	22	22	75	3.4 ($p < 0.001$)	20 (90.9)	9 (41)	8 (36)
Female	1	40	80	2 (NA)	1 (100)	0 (0)	0 (0)
		$p = 0.537$	$p = 0.814$	$p = 1.000$	$p = 1.000$	$p = 1.000$	$p = 1.000$
Pre-vaccination titer							
<1:10	5	5	35	7.0 ($p = 0.009$)	3 (60)	4 (80)	3 (60)
1:10–1:20	8	17	135	8.0 ($p = 0.003$)	8 (100)	5 (63)	5 (63)
≥1:40	10	61	70	1.1 ($p = 0.168$)	10 (100)	0 (0)	0 (0)
		$p < 0.001$	$p = 0.146$	$p < 0.001$	$p = 0.020$	$p = 0.001$	$p = 0.008$
Immune checkpoint inhibitor							
Pembrolizumab	10	23	53	2.3 ($p = 0.024$)	8 (80)	3 (30)	2 (20)
Atezolizumab	7	24	108	4.4 ($p = 0.047$)	7 (100)	3 (43)	3 (43)
Durvalumab	5	26	106	4.0 ($p = 0.129$)	5 (100)	2 (40)	2 (40)
Nivolumab	1	5	40	8 (NA)	1 (100)	1 (100)	1 (100)
		$p = 0.580$	$p = 0.423$	$p = 0.711$	$p = 0.526$	$p = 0.683$	$p = 0.426$

For statistical analysis, the Wilcoxon rank-sum test, Wilcoxon signed-rank test, Fisher's exact test, Kruskal–Wallis test, Jonckheere–Terpstra test, or Cochran–Armitage test was performed as appropriate. Results with $P < 0.05$ were considered significant.
NA, not applicable.

previously reported values [17,21,27]. A study on the immunogenicity and safety of a quadrivalent influenza vaccine in Japan referenced in Table 3 also reported low sC because of high antibody prevalence pre-vaccination [25].

Furthermore, a previous study reported that adverse reactions to a quadrivalent influenza vaccine in healthy subjects included 22% systemic and 26% local reactions [22]. In another study involving healthy individuals, adverse reactions were recorded as follows—systemic reactions: fever 1.3%, fatigue 16.7%, joint pain 3.8%, and headache 3.8% and local reactions: redness/swelling 80.8%, itching 12.8%, and pain 73.1% [25]. The incidence of redness/swelling and pain was high, but this could be because the study participants were healthcare providers who might have observed adverse effects more meticulously and potentially reported them excessively. In our study, which involved patients with lung cancer receiving ICIs, the incidence of systemic reactions was 29% (fever 0%, fatigue 21%, joint pain 13%, and headache 8%) and that of local reactions was 21% (redness 13%, swelling 17%, itching 4%, and pain 13%). The majority of these reactions were of grade 1 and all adverse reactions improved within a few days. Therefore, the adverse reactions to influenza vaccination in patients with lung cancer who were receiving ICIs were similar to those in healthy subjects in the previous study and were therefore considered acceptable. In addition, the number of irAEs due to treatment with ICIs did not increase after influenza vaccination [16,18]. Consistent with these results, in the

Table 6
Immunogenicity of B(Yamagata) strain influenza vaccine in patients with lung cancer receiving immune checkpoint inhibitor treatment.

		Geometric mean titer		Mean fold rise (S1/S0)	Post-vaccination		
	N	Pre-vaccination (S0)	Post-vaccination (S1)		Seroprotection rate Post-vaccination (sP) (1 ≥ 1:40): n (%)	Seroresponse rate (sR) (≥4-fold-rise): n (%)	Seroconversion rate (sC)
Age (years)							
<70	11	27	97	3.5 ($p = 0.006$)	10 (91)	3 (27)	3 (27)
≥70	12	18	32	1.8 ($p = 0.085$)	6 (50)	3 (25)	3 (25)
		$p = 0.157$	$p = 0.020$	$p = 0.044$	$p = 0.069$	$p = 1.000$	$p = 1.000$
Sex							
Male	22	22	55	3.3 ($p < 0.001$)	15 (68.2)	6 (27)	6 (27)
Female	1	20	40	2 (NA)	1 (100)	0 (0)	0 (0)
		$p = 1.000$	$p = 0.939$	$p = 0.874$	$p = 1.000$	$p = 1.000$	$p = 1.000$
Pre-vaccination titer							
1:10–1:20	15	14	44	3.0 ($p = 0.007$)	8 (53)	5 (33)	5 (33)
≥1:40	8	48	80	1.7 ($p = 0.020$)	8 (100)	1 (13)	1 (13)
		$p < 0.001$	$p = 0130$	$p = 0.586$	$p = 0.052$	$p = 0.369$	$p = 0.369$
Immune checkpoint inhibitor							
Pembrolizumab	10	20	46	2.3 ($p = 0.051$)	7 (70)	3 (30)	3 (30)
Atezolizumab	7	30	88	3.0 ($p = 0.042$)	5 (71)	2 (29)	2 (29)
Durvalumab	5	20	26	1.3 ($p = 0.178$)	3 (60)	0 (0)	0 (0)
Nivolumab	1	10	320	32 (NA)	1 (100)	1 (100)	1 (100)
		$p = 0.865$	$p = 0.552$	$p = 0.865$	$p = 1.000$	$p = 0.276$	$p = 0.276$

For statistical analysis, the Wilcoxon rank-sum test, Wilcoxon signed-rank test, Fisher's exact test, or Kruskal–Wallis test was performed as appropriate. Results with $P < 0.05$ were considered significant.
NA, not applicable.

Table 7
Immunogenicity of B(Victoria) strain influenza vaccine in patients with lung cancer receiving immune checkpoint inhibitor treatment.

		Geometric mean titer		Mean fold rise (S1/S0)	Post-vaccination		
	N	Pre-vaccination (S0)	Post-vaccination (S1)		Seroprotection rate (sP) (1 ≥ 1:40): n (%)	Seroresponse rate (sR) (≥4-fold-rise): n (%)	Seroconversion rate (sC)
Age (years)							
<70	11	11	33	2.9 ($p = 0.009$)	6 (55)	3 (27)	3 (27)
≥70	12	9	32	3.6 ($p = 0.002$)	6 (50)	5 (42)	4 (33)
		$p = 0.412$	$p = 1.000$	$p = 0.647$	$p = 1.000$	$p = 0.667$	$p = 1.000$
Sex							
Male	22	10	32	3.2 ($p < 0.001$)	11 (50)	7 (32)	6 (27)
Female	1	10	40	4 (NA)	1 (100)	1 (100)	1 (100)
		$p = 1.000$	$p = 0.755$	$p = 0.521$	$p = 1.000$	$p = 0.348$	$p = 0.304$
Pre-vaccination titer							
<1:10	7	5	40	8.0 ($p = 0.007$)	4 (57)	5 (71)	4 (57)
1:10–1:20	15	13	29	2.3 ($p < 0.001$)	7 (47)	3 (20)	3 (20)
≥1:40	1	40	40	1.0 (NA)	1 (100)	0 (0)	0 (0)
		$p < 0.001$	$p = 0.386$	$p = 0.725$	$p = 0.918$	$p = 0.016$	$p = 0.063$
Immune checkpoint inhibitor							
Pembrolizumab	10	9	25	2.8 ($p = 0.005$)	4 (40)	4 (40)	3 (30)
Atezolizumab	7	15	49	3.3 ($p = 0.037$)	6 (86)	2 (29)	2 (29)
Durvalumab	5	8	35	4.6 ($p = 0.086$)	2 (40)	2 (40)	2 (40)
Nivolumab	1	10	20	2 (NA)	0 (0)	0 (0)	0 (0)
		$p = 0.224$	$p = 0.376$	$p = 0.224$	$p = 0.130$	$p = 1.000$	$p = 1.000$

For statistical analysis, the Wilcoxon rank-sum test, Wilcoxon signed-rank test, Fisher's exact test, Kruskal–Wallis test, Jonckheere–Terpstra test, or Cochran–Armitage test was performed as appropriate. Results with $P < 0.05$ were considered significant.
NA, not applicable.

present study, irAEs were low at 4% (grade 2) during the 6 months post-vaccination.

In addition to previous studies, the significant increase in GMT for all strains, high sP, and the absence of an increase in the number of adverse reactions or irAEs in this study may support influenza vaccination in patients with lung cancer who are receiving ICIs. Although studies on the clinical outcomes of influenza vaccine in these patients are still limited, a recent large multicenter prospective study reported a significant reduction in influenza-related complications with vaccination [28]. However, further studies are required to evaluate influenza vaccination's immunogenicity and clinical outcomes in patients with cancer who are receiving ICIs. The administration of a combination of cytotoxic anticancer drugs and ICIs has increased in recent years; therefore, further studies are required to determine the immunogenicity and effectiveness of influenza vaccines in patients receiving these therapies.

Our study has several limitations. First, the sample size was small, although the minimum requirement was met. Patient enrollment was limited by the short period between when the influenza vaccine became available and vaccination before the expected winter influenza epidemic. The inclusion of a larger number of patients may provide more representative results, especially when considering the effects of different ICI regimens in patients with lung cancer. Second, in our study, asymptomatic infections could have co-occurred. We monitored all patients for influenza-like illnesses and no patient confirmed influenza

Table 8
Adverse events in patients with lung cancer receiving immune checkpoint inhibitor treatment post-vaccination.

	Patients (N = 24); n (%)
Systemic events	
Any	7 (29)
Fever	0 (0)
Fatigue	5 (21)
Joint pain	3 (13)
Headache	2 (8)
Rash	2 (8)
Local reactions	
Any	5 (21)
Redness	3 (13)
Swelling	4 (17)
Induration	3 (13)
Itch	1 (4)
Pain	3 (13)

during the study period. Therefore, concurrent infection was not sufficiently evident to invalidate the obtained results. Third, we did not recruit healthy controls in this study. However, we have referenced the data of healthy individuals from a previous study [25]. Regarding the B/Phuket/3073/2013 (Yamagata) strain, which was included in the vaccines in both this study and the previous study, the sP values were equivalent, suggesting comparable immunogenicity. Although strains other than A(H3N2) did not meet the FDA criteria, all strains met the EMA criteria. Given the tolerable adverse events, this study supports influenza vaccination in the study population. Fourth, as mentioned, the high proportion of the pre-vaccination antibody titers $\geq$1:40 of the study population may have affected the high sP. The high pre-vaccination titers may be because of high influenza vaccination coverage and previous undiagnosed infection in this population. In Japan, the annual influenza vaccination coverage among elderly individuals is high, approximately 70% [29]. Similar results may not be obtained in a population with low pre-vaccination antibody titers.

5. Conclusions

In this study, influenza vaccination in patients with lung cancer receiving ICIs resulted in a significant increase in GMT for all strains and a high sP (52%–91%). The adverse reactions and irAEs were considered acceptable. The study results support the recommendation for annual influenza vaccination in this population. Further studies assessing influenza vaccine effectiveness in these patients are required to strengthen the evidence supporting influenza vaccination.

Funding

This study was supported by a scholarship donation from ONO PHARMACEUTICAL CO., LTD.

Declaration of interest

K.N. received a scholarship donation from ONO PHARMACEUTICAL CO., LTD.

Author contribution

K.N. was responsible for conceptualization, data curation, formal analysis, investigation, resources, methodology, project administration, software, validation, and visualization. H.Y., J.T., N.K., A.O., H.I., and Y. O. were responsible for investigation and resources. K.K. was responsible for resources. S.O. and W.F. were responsible for conceptualization, methodology, and formal analysis. Y.H. was responsible for conceptualization, funding acquisition, methodology, and supervision. All authors contributed to the writing of the final manuscript. All authors have read and approved the final draft of the article.

Availability of data and materials

The data supporting the findings of this study are available from the corresponding author upon reasonable request. The data are not publicly available because of privacy and ethical restrictions.

Acknowledgments

We thank the staff of the Department of Pulmonology and Clinical Laboratory at Kameda Medical Center for their involvement in this study.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jiac.2023.07.008.

References

[1] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA A Cancer J Clin 2021;71:209–49. https://doi.org/10.3322/caac.21660.
[2] Howlader N, Forjaz G, Mooradian MJ, Meza R, Kong CY, Cronin KA, et al. The effect of advances in lung-cancer treatment on population mortality. N Engl J Med 2020;383:640–9. https://doi.org/10.1056/nejmoa1916623.
[3] Hanna NH, Schneider BJ, Temin S, Baker S, Brahmer J, Ellis PM, et al. Therapy for stage IV non–small-cell lung cancer without driver alterations: ASCO and OH (CCO) joint guideline update. J Clin Oncol 2020;38:1608–32. https://doi.org/10.1200/jco.19.03022.
[4] Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. N Engl J Med 2018;378:158–68. https://doi.org/10.1056/NEJMra1703481.
[5] Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, et al. Pembrolizumab versus chemotherapy for PD-L1–positive non–small-cell lung cancer. N Engl J Med 2016;375:1823–33. https://doi.org/10.1056/nejmoa1606774.
[6] Herbst RS, Giaccone G, De Marinis F, Reinmuth N, Vergnenegre A, Barrios CH, et al. Atezolizumab for first-line treatment of PD-L1–selected patients with NSCLC. N Engl J Med 2020;383:1328–39. https://doi.org/10.1056/nejmoa1917346.
[7] Hellmann MD, Paz-Ares L, Bernabe Caro R, Zurawski B, Kim S-W, Carcereny Costa E, et al. Nivolumab plus ipilimumab in advanced non–small-cell lung cancer. N Engl J Med 2019;381:2020–31. https://doi.org/10.1056/nejmoa1910231.
[8] Socinski MA, Jotte RM, Cappuzzo F, Orlandi F, Stroyakovskiy D, Nogami N, et al. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. N Engl J Med 2018;378:2288–301. https://doi.org/10.1056/NEJMoa1716948.
[9] Gandhi L, Rodriguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. N Engl J Med 2018;378:2078–92. https://doi.org/10.1056/NEJMoa1801005.
[10] Taha A, Vinograd I, Sakhnini A, Eliakim-Raz N, Farbman L, Baslo R, et al. The association between infections and chemotherapy interruptions among cancer patients: prospective cohort study. J Infect 2015;70:223–9. https://doi.org/10.1016/j.jinf.2014.10.008.
[11] Cooksley CD, Avritscher EBC, Bekele BN, Rolston KV, Geraci JM, Elting LS. Epidemiology and outcomes of serious influenza-related infections in the cancer population. Cancer 2005;104:618–28. https://doi.org/10.1002/cncr.21203.
[12] Rubin LG, Levin MJ, Ljungman P, Davies EG, Avery R, Tomblyn M, et al. IDSA clinical practice guideline for vaccination of the immunocompromised host. Clin Infect Dis : an official publication of the Infectious Diseases Society of America 2013;2014(58):309–18. https://doi.org/10.1093/cid/cit816.
[13] Grohskopf LA, Alyanak E, Ferdinands JM, Broder KR, Blanton LH, Talbot HK, et al. Prevention and control of seasonal influenza with vaccines: recommendations of the advisory committee on immunization practices, United States, 2021–22 influenza season. MMWR Recomm Rep (Morb Mortal Wkly Rep) 2021;70:1–28. https://doi.org/10.15585/mmwr.rr7005a1.
[14] Nakashima K, Aoshima M, Ohfuji S, Suzuki K, Katsurada M, Katsurada N, et al. Immunogenicity of trivalent influenza vaccine in patients with lung cancer undergoing anticancer chemotherapy. Hum Vaccines Immunother 2017;13:543–50. https://doi.org/10.1080/21645515.2016.1246094.
[15] Bitterman R, Eliakim-Raz N, Vinograd I, Zalmanovici Trestioreanu A, Leibovici L, Paul M. Influenza vaccines in immunosuppressed adults with cancer. Cochrane Database Syst Rev 2018;2:CD008983. https://doi.org/10.1002/14651858.CD008983.pub3.
[16] Spagnolo F, Boutros A, Croce E, Cecchi F, Arecco L, Tanda E, et al. Influenza vaccination in cancer patients receiving immune checkpoint inhibitors: a systematic review. Eur J Clin Invest 2021;51:e13604. https://doi.org/10.1111/eci.13604.

[17] Keam B, Kang CK, Jun KI, Moon SM, Suh KJ, Lee DW, et al. Immunogenicity of influenza vaccination in patients with cancer receiving immune checkpoint inhibitor. Clin Infect Dis : an official publication of the Infectious Diseases Society of America 2019. https://doi.org/10.1093/cid/ciz1092.
[18] Chong CR, Park VJ, Cohen B, Postow MA, Wolchok JD, Kamboj M. Safety of inactivated influenza vaccine in cancer patients receiving immune checkpoint inhibitors. Clin Infect Dis 2020;70:193–9. https://doi.org/10.1093/cid/ciz202.
[19] Hirst GK. The quantitative determination of influenza virus and antibodies by means of red cell agglutination. J Exp Med 1942;75:49–64. https://doi.org/10.1084/jem.75.1.49.
[20] Schneider BJ, Naidoo J, Santomasso BD, Lacchetti C, Adkins S, Anadkat M, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: ASCO guideline update. J Clin Oncol : official journal of the American Society of Clinical Oncology 2021;39:4073–126. https://doi.org/10.1200/JCO.21.01440.
[21] Laubli H, Balmelli C, Kaufmann L, Stanczak M, Syedbasha M, Vogt D, et al. Influenza vaccination of cancer patients during PD-1 blockade induces serological protection but may raise the risk for immune-related adverse events. J Immunother Cancer 2018;6:40. https://doi.org/10.1186/s40425-018-0353-7.
[22] Tsurudome Y, Kimachi K, Okada Y, Matsuura K, Ooyama Y, Ibaragi K, et al. Immunogenicity and safety of an inactivated quadrivalent influenza vaccine in healthy adults: a phase II, open-label, uncontrolled trial in Japan. Microbiol Immunol 2015;59:597–604. https://doi.org/10.1111/1348-0421.12316.
[23] Moa AM, Chughtai AA, Muscatello DJ, Turner RM, MacIntyre CR. Immunogenicity and safety of inactivated quadrivalent influenza vaccine in adults: a systematic review and meta-analysis of randomised controlled trials. Vaccine 2016;34:4092–102. https://doi.org/10.1016/j.vaccine.2016.06.064.
[24] Centor for Biologics Evaluation and Research Guidance for Industry. Clinical data needed to support the licensure of seasonal inactivated influenza vaccines. Food and Drug Administration; 2007. http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm074786.htm. [Accessed 17 July 2020].
[25] Naoaki Watanabe NO, Nagai Hideaki, Kato Takafumi, Saito Minako, Igarashi Ayaka, Suzukawa Maho, et al. Immunogenicity and safety of an inactivated quadrivalent influenza vaccine in healthy adults in Japan. Annals of the Japanese Respiratory Society 2018;7:197–203.
[26] European Committee for Proprietary Medial Products. Notefor guidance on harmmonisation of requirements for in-fluenza vaccines. London: EuropeanAgency for the Evaluation of Medical Products; 1997 (CPMP/BWP/214/96), http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003945.pdf. [Accessed 18 June 2023].
[27] Bayle A, Khettab M, Lucibello F, Chamseddine AN, Goldschmidt V, Perret A, et al. Immunogenicity and safety of influenza vaccination in cancer patients receiving checkpoint inhibitors targeting PD-1 or PD-L1. Ann Oncol : official journal of the European Society for Medical Oncology 2020;31:959–61. https://doi.org/10.1016/j.annonc.2020.03.290.
[28] Bersanelli M, Giannarelli D, De Giorgi U, Pignata S, Di Maio M, Clemente A, et al. INfluenza Vaccine Indication during therapy with Immune checkpoint inhibitors: a multicenter prospective observational study (INVIDIa-2). Journal for ImmunoTherapy of Cancer 2021;9:e002619. https://doi.org/10.1136/jitc-2021-002619.
[29] Kaneko M, Aoki T, Goto R, Ozone S, Haruta J. Better patient experience is associated with better vaccine uptake in older adults: multicentered cross-sectional study. J Gen Intern Med 2020;35:3485–91. https://doi.org/10.1007/s11606-020-06187-1.