# Respiratory tract infection: prevention, early detection and attenuation of immune response

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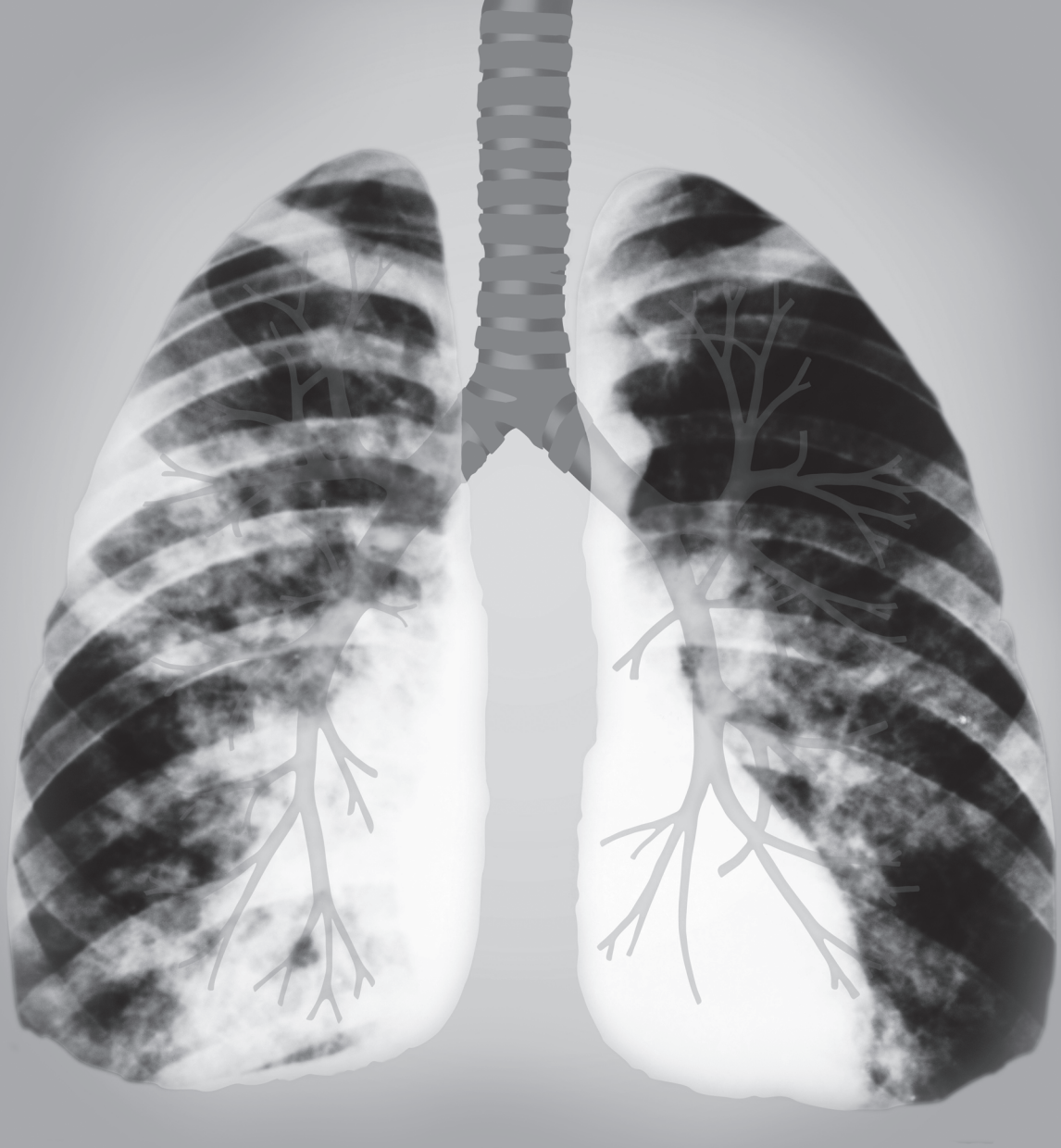

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# Influenza vaccination in patients with lung cancer receiving anti-programmed death receptor 1 immunotherapy does not induce immune-related adverse events.

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## ABSTRACT

### Background

Influenza vaccination is recommended in cancer patients to reduce influenza-related complications. Recently more immune related adverse events (irAE) were demonstrated in lung cancer patients who were vaccinated with the trivalent seasonal influenza vaccine during anti-PD1 immunotherapy. Confirmation of these findings is essential before recommendations on influenza vaccination may be revoked.

### Methods

In this cohort study in lung cancer patients receiving nivolumab 3 mg/kg every two weeks during two influenza seasons (2015/16 – 2016/17) irAEs have been monitored. Incidence, timing and severity of irAEs were compared between vaccinated patients and non-vaccinated patients.

### Findings

In a compassionate use program 127 lung cancer patients had been treated with at least one dose of nivolumab during two national influenza vaccination campaigns from September until December of 2015 and 2016. Forty-two patients had received the influenza vaccine and 85 patients were not vaccinated. Median follow up period was 118 days (IQR 106-119). Mean age was 64 years (range 46-83).

In vaccinated and non-vaccinated patients the incidence of irAEs was 26% and 22%, respectively, rate ratio 1.20 (95% CI 0.51 – 2.65). The incidence of serious irAEs was 7% and 4%, respectively, rate ratio 2.07 (95% CI 0.28 – 15.43). Influenza vaccination during nivolumab did not result in significant differences in rates of discontinuation, death, clinical deterioration or tumour response between groups.

### Interpretation

Influenza vaccination in lung cancer patients receiving anti-PD-1 immunotherapy does not induce immune related adverse events in our cohort. With this result, influenza vaccination should not be deterred from this group of patients.

## INTRODUCTION

Immunotherapy has become a standard novel treatment option for several malignancies and across all tumour stages. The immune system plays a critical role in fighting off cancer by detecting and controlling the proliferation of malignant cells.[1] CD8+ T cells are key players in the anti-tumour immune response and these cells have therefore been an important target for immunotherapeutic interventions. Immune checkpoints on activated T cells are inhibitory pathways that modulate the intensity and the extent of the immune response, preventing persistent immune activation and autoimmunity.[2] The anti-tumour response of the immune system can be enhanced by blocking these checkpoint inhibitors by use of antibodies against CTLA-4 (ipilimumab), programmed death receptor 1 (PD-1) (nivolumab and pembrolizumab) and its ligands (PD-L1 (atezolizumab, avelumab, durvalumab) and PD-L2.[2,3] Currently approved indications include melanoma, renal cell carcinoma, non-small cell lung cancer, urothelial carcinoma, head and neck cancer, Merkel cell carcinoma and Hodgkin's lymphoma, and new indications are under investigation.[4]



Anti-PD1 induced stimulation of the immune system can cause immune-related adverse events in 0.2-5.6% per organ system.[5] Immune-related adverse events (irAEs) are affecting the endocrine organs, skin, colon, liver, lungs, kidney and pancreas, but all other organs may be affected.[6] Although it is believed that the adverse events are a result of the disrupted immunologic homeostasis, the exact pathogenesis is still poorly understood.[7] Furthermore, flares of underlying autoimmune disease have been documented in patients receiving checkpoint inhibitors.[8]

Cancer patients are eligible for influenza vaccination due to their increased risk of developing complications when infected with seasonal influenza viruses and because influenza infections result in interruptions of cancer treatment.[9] Patient with lung cancer commonly have additional reduction of pulmonary function due to COPD and would benefit from influenza vaccination.[10] Additionally, symptoms caused by respiratory tract infections such as influenza infection can be similar in presentation to pulmonary immune-related adverse events, posing therapeutic dilemmas about continuation of immunotherapy or initiation of immunosuppressive agents to alleviate irAEs. Finally, since it was found that antibiotic use or change in microbioma may inhibit the clinical benefit of checkpoint inhibitors, interventions during immunotherapy should be applied that reduce the chance of febrile episodes leading to undesired administration of empiric antibiotics.[11] In order to reduce the possibility of influenza virus infection to cause a clinical deterioration in patients with multiple pulmonary co-morbidities and because of above mentioned considerations, seasonal influenza vaccination of patients treated with chemotherapy should be strongly advocated.[12]

It is not known whether administration of additional antigens to cancer patients receiving immunotherapy, for example due to vaccination, may result in a higher incidence of vaccine-related adverse events or (serious) irAEs. Recently, Läubli and colleagues demonstrated an unexpected high incidence of 52% of irAEs in a cohort of 23 patients undergoing treatment with PD-1/PD-L1 antibodies.[13] Influenza vaccination proved to be immunogenic during anti-PD1 immunotherapy, because no differences between patients and healthy controls in vaccine-induced antibody titers against the included influenza antigens were observed.

Confirmation of these findings in larger cohorts is required and should clarify whether the reported results in a small number of subjects should translate into a deferral or even a contra-indication of influenza vaccination, which is a universally recommended measure in cancer patients to decrease influenza-related complications. Therefore, we investigated the effect of the influenza vaccination on the incidence of irAEs in a uniform cohort of lung cancer patients undergoing checkpoint blockade treatment with antibodies against PD-1.

## MATERIALS AND METHODS

We performed a cohort study comparing the incidence of irAEs and serious irAEs in the influenza vaccinated subgroup versus the unvaccinated subgroup. Ethical approval was obtained from the Medical Ethical Committee of the Antoni van Leeuwenhoek Hospital in Amsterdam, the Netherlands.

### Study Population

Patients were identified in the nivolumab compassionate use program database of the Antoni van Leeuwenhoek hospital in Amsterdam. This database contains demographic data and prospectively collected clinical course and response data of patients with advanced lung cancer receiving intravenous administration of nivolumab 3 mg/kg every two weeks. Patients who had been administered at least one dose of nivolumab during the influenza vaccination seasons between September 1st and January 1st of 2015-16 or 2016-17 were enrolled. In the Netherlands, persons at risk from complications of influenza infections - all people aged 60 year or older and people with specified chronic diseases - are invited by their general practitioner for vaccination with a trivalent inactivated influenza vaccine free of charge between October and December.

The influenza vaccination status of the patients was obtained retrospectively via a short questionnaire sent to the general practitioners of those patients. Patients were included in the vaccinated group if they received an influenza vaccination after they started the

nivolumab treatment or if they were vaccinated at most 30 days before receiving the first dose of nivolumab. All other patients, including those who had been vaccinated more than 30 days before receiving the first dose of nivolumab, were included in the non-vaccinated group.

## Assessment

Demographic data, medical history, tumour stage at the start of treatment, adverse events, the grade of the adverse events and the tumour response after vaccination were evaluated. From date of vaccination, the follow-up period was until March 1st of the following year. Non-vaccinated patients were included as controls with an identical follow-up period to determine the incidence of irAEs: the median date of influenza vaccination in the other group until March 1st of the following year. Adverse events were classified in irAEs and non-immune-related adverse events (non-irAE) by two investigators, unaware of the vaccination status, according to the classification criteria described by J.B.A.G. Haanen and colleagues.[14] The incidence of irAEs in influenza vaccinated group versus unvaccinated group is the primary outcome. Secondary outcome measures were grading of the adverse events, incidence of serious irAEs and non-irAEs and tumour effect. Grading of the adverse events was done according to the Common Terminology Criteria for Adverse Events, version 4.0. Possible effects on the tumour response were assessed with the use of the Response Evaluation Criteria in Solid Tumours.[15] For this assessment, the first available CT-scan after the vaccination date, or median vaccination date in the control group, was compared to the latest CT-scan before this date.



## Statistical analysis

Descriptive statistics of baseline demographic and clinical characteristics were composed both for the vaccinated and for the unvaccinated group. Variables were checked for normality and means or medians were calculated accordingly. Differences in the average age and average time until irAEs occurred between both groups were analysed by independent sample t-tests. Treatment duration was compared using Mann-Whitney U tests and ordered logistic regression was used to compare the treatment response of the two groups.

Differences in the rate of adverse events, irAEs and serious irAEs, differences in sex and differences in treatment discontinuity between the two study groups were analysed by Fisher exact tests and Chi square tests. SPSS version 23 was used for statistical analyses.

## RESULTS

The compassionate use program database included a total of 213 patients with non-small cell lung cancer who underwent treatment with nivolumab. Four patients contributed twice because they received nivolumab treatment during the inclusion window both in 2015 and in 2016. The total number of eligible cases was therefore 217. From this cohort, 131 cases had been administered at least one dose of nivolumab between September 1st and January 1st. From these 131 cases, 42 had been vaccinated: four before receiving the first dose of nivolumab (median 11, range 1 – 26 days), 33 during treatment with nivolumab and five after receiving the final dose of nivolumab (median 26, range 20 – 61 days). For four cases the vaccination states could not be retrieved (Figure 1.). The median vaccination date was November 2nd.

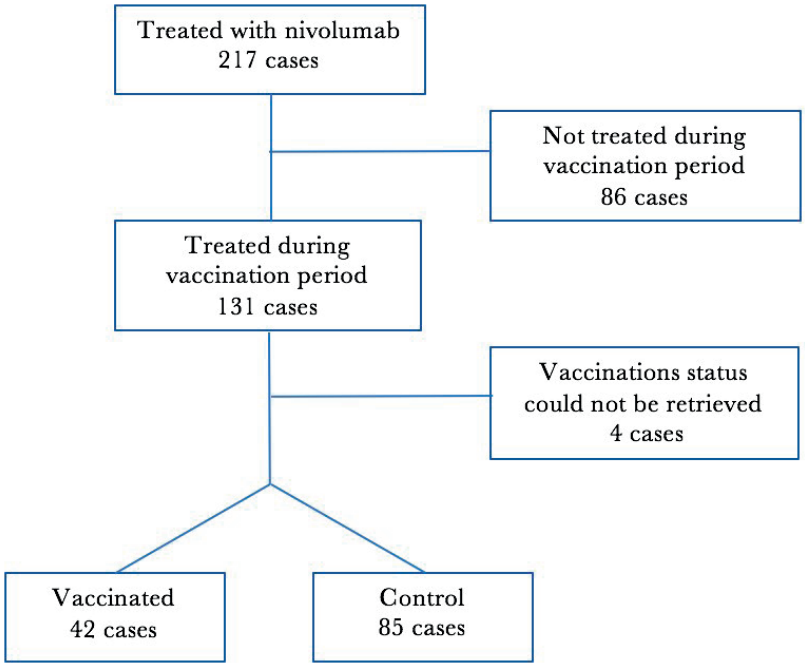


**Figure 1.** Flowchart of selection process.

The final analysis consisted therefore of 42 cases in the vaccinated group and 85 cases in the control group. Baseline characteristics are shown in table 1. The study population had a mean age of 63 years. The vaccinated group was marginally older than the unvaccinated group, but the difference reached significance. No significant differences were found in sex, treatment duration and treatment intensity between the vaccinated group and the control group.

**Table 1.** Baseline characteristics of the patients receiving immunotherapy, contrasting those who were vaccinated with trivalent inactivated influenza vaccine and those who were not vaccinated.

| | Total n=127 | Vaccinated n=42 | Control n=85 | p-value |
|---|---|---|---|---|
| Mean age (95% CI)[a] | 62.6 (61.2 – 64.1) | 64.8 (62.4 – 67.1) | 61.6 (59.7 – 63.5) | 0.04 |
| Male | 61 (48.0%) | 23 (54.8%) | 38 (44.7%) | 0.29 |
| Clinical stage | | | | 0.70 |
| III | 6 (4.7%) | 1 (2.4%) | 5 (5.9%) | |
| III/IV | 2 (1.6%) | 1 (2.4%) | 1 (1.2%) | |
| IV | 119 (93.7%) | 40 (95.2%) | 79 (92.9%) | |
| Median nr. of cycles nivolumab received at vaccination/start FU[b] (IQR)[c] | 5.5 (3 – 12)[d] | 4.5 (2 – 14)[e] | 6 (3 – 12)[f] | 0.66 |
| Median treatment duration in days at vaccination /start FU[b] (IQR)[c] | 78 (28 – 174)[d] | 58.5 (18 – 211)[e] | 81.5 (40 – 165)[f] | 0.60 |
| Median nr. of cycles nivolumab received at end FU[b] (IQR)[c] | 9 (5 – 15) | 9.5 (4 – 18) | 9 (6 – 14) | 0.71 |
| Median treatment duration in days at end FU[b] (IQR)[c] | 132 (70 – 222) | 125 (39 – 281) | 134 (72 – 213) | 0.95 |

a 95% confidence interval
b Follow-up
c Interquartile range
d 106 cases eligible
e 38 cases eligible
f 68 cases eligible

The median follow-up duration did not differ significantly between both groups. (107 and 118 days in the vaccinated and control group, respectively)

In the vaccinated group, 11 irAEs were observed during follow up (incidence of 26%), whilst 19 irAEs were found in the control group (incidence of 22%). The vaccinated group was not at a significantly higher risk of developing irAEs, rate ratio 1.20 (95% confidence interval 0.51 – 2.65). The most commonly observed immune-related adverse events were toxicities of the endocrine organs (incidence of 8%), followed by pulmonary adverse events. Also the risk of serious irAEs (grade 3-5) was not significantly higher in the vaccinated group compared to the control group, rate ratio 2.07 (95% confidence interval 0.28 – 15.43). Three serious irAEs were found both in the vaccinated group (incidence of 7%) and in the control group (incidence of 4%) (Table 2).

A sub-analysis was done excluding the four cases that had been vaccinated in the 30 days before the first dose of nivolumab. Thirty-eight cases from the vaccinated group remained eligible. Also in this analysis, no significant increased risk was found for developing irAEs, rate ratio 1.20 (95% confidence interval 0.50 – 2.71) or serious irAEs, rate ratio 1.52 (95% confidence interval 0.13 – 13.25).

**Table 2.** Outcome parameters

| | Total n=127 [13393 days][a] | Vaccinated n=42 [4367 days][a] | Control n=85 [9026 days][a] | Rate Ratio [CI-interval] |
|---|---|---|---|---|
| Adverse events | 67 (53%) | 22 (52%) | 45 (53%) | 1.01 [0.58 – 1.71] |
| irAEs (all grades) | 30 (24%) | 11 (26%) | 19 (22%) | 1.20 [0.51 – 2.65] |
| Endocrine | | 3 (7%) | 7 (8%) | |
| Pulmonary | | 4 (10%) | 4 (5%) | |
| Gastrointestinal | | 1 (2%) | 2 (2%) | |
| Hepatic | | 1 (2%) | 2 (2%) | |
| Arthritis | | 1 (2%) | 1 (1%) | |
| Neurological | | 1 (2%) | 0 | |
| Skin | | 0 | 1 (1%) | |
| Other | | 0 | 2 (2%) | |
| Serious irAEs (grade 3-5) | 6 (5%) | 3 (7%) | 3 (4%) | 2.07 [0.28 – 15.43] |
| Gastrointestinal | | 1 (2%) | 1 (1%) | |
| Hepatic | | 1 (2%) | 1 (1%) | |
| Neurological | | 1 (2%) | 0 | |
| Skin | | 0 | 1 (1%) | |
| Outcome | | | | |
| Death | 26 (20%) | 11 (26%) | 15 (18%) | p = 0.26[b] |
| Discontinuation due to irAEs | 6 (5%) | 2 (5%) | 4 (5%) | p = 1.00[b] |
| Discontinuation due to progression or clinical deterioration | 62 (49%) | 21 (50%) | 41 (48%) | p = 0.85[b] |

a Total person-time in follow-up
b P-value fisher exact test

A second sub-analysis was done including only those patients that had been vaccinated in between bi-weekly infusions with nivolumab (n=33). No significant increased risk was found for developing irAEs, rate ratio 1.33 (95% confidence interval 0.55 – 3.01) or serious irAEs, rate ratio 1.69 (95% confidence interval 0.14 – 14.72).

Furthermore, the total number of adverse events showed no significant differences between the vaccinated group and the controls, rate ratio 1.01 (95% confidence interval 0.58 – 1.72). No significant difference was observed in the time until irAEs occurred as well. In the vaccinated group, the mean time from the date of vaccination until a first irAE occurred was 47.6 days, whereas in the control group, the mean time until a first irAE occurred was 58.7 days (p=0.41, 95% CI -38.67 – 16.45).

No difference in treatment discontinuation as a result of irAEs was found between both groups. The total number of patients that had stopped their nivolumab therapy at the end

of the follow-up period (due to irAEs or clinical deterioration or progression) was similar in both groups (55% in the vaccinated groups versus 53% in the control group, p=0.85). Tumour response and mortality did not differ between both groups.

To control for the difference in age between the two study groups, a sub-analysis was performed including patients above the age of 50 only: 41 patients in the vaccinated group and 75 patients in the control group. Mean age was not significantly different between groups (p=0.22). In this subgroup, the vaccinated cases were not at higher risk for developing irAEs, rate ratio 1.36 (95% confidence interval 0.58 – 3.16) or serious irAEs, rate ratio 1.86 (95% confidence interval 0.25 – 13.86) compared to the controls.



## DISCUSSION

Our study demonstrates that there is no significant difference in the likelihood of immune-related adverse events and serious immune-related adverse events between patients who have received influenza vaccination and in patients without. Furthermore, no significant differences in treatment outcome, discontinuation rates or tumour response were observed between the two groups.

The overall incidence of irAEs found in our study (24%) is comparable with the incidence of 26.5% found by El Osta et al. in a meta-analysis including 1259 patients treated with antibodies against PD-1.[16] Furthermore, the rate of serious irAEs found in our study (5%) is consistent with the 7% rate found in this meta-analysis. Our study experienced little drop-out with only four cases missing in the final analysis and the results of sub-analyses were consistent with our general findings. Further strengths of our study are a uniform cancer type and stage and a single drug being explored.

Our study had some limitations that are inherent to the design of the study. We did not collect anti-influenza antibodies or immunological markers to elucidate the markers associated with the development of irAEs. Due to the period of observation of five months at most, the occurrence of late sequelae could not be determined. However, due to the immunologic rationale underlying the potential increase in irAEs, it is expected that irAEs would occur within the usual time frame. Since registration of vaccine-related adverse events was missing, a potential increase in reactogenicity of the vaccine cannot be ruled out. Possible influenza infections during treatment were not monitored and therefore vaccine effectiveness cannot be established in our cohort. Vaccine effectiveness will likely be preserved, because the study by Läubli et al. did not observe significant differences between patients treated with checkpoint inhibitors and healthy controls in vaccine-induced

antibody titers against all tree viral antigens of the inactivated influenza vaccine.[13] Furthermore, the number of temporary interruptions of immunotherapeutic treatment because of influenza-related complications was not measured in this study. The vaccinated group was on average three years older than the control group, but in sub-analyses including only older patients similar outcomes regarding the risk of adverse events were found, strengthening our assumption that the small difference in age is unlikely to have influenced our results. Finally, we do not know the reason for not vaccinating the patients in the control group. Notwithstanding, we believe it is unlikely that the unknown reason would have affected the incidence of irAEs.

With the increased sample size of our study, we could not confirm the findings in the small study by Läubli and colleagues who reported a statistically significant increased rate of immune-related adverse events in patients who received an influenza vaccination whilst undergoing checkpoint blockade. However, our study does not provide a definitive answer, because it is underpowered to detect a very small, but significant increase in the risk of irAEs.

The immunological mechanisms potentially associated with an increased risk of irAEs when patients receiving checkpoint inhibitors are vaccinated with the non-adjuvanted inactivated influenza vaccine are not clear. Whether vaccines induce or aggravate autoimmunity has been debated at length without a definitive verdict, but accidental reports do hint at that association, potentially related to particular adjuvants, described as the autoimmune/inflammatory syndrome induced by adjuvants (ASIA syndrome).[17] However, the trivalent inactivated influenza vaccine does not contain adjuvants. Therefore, considering the uncertainties about the aetiology of autoimmune phenomena related to vaccination, whether pathophysiological pathways resulting in these vaccine-related adverse events coincide with those in irAEs related to checkpoint inhibitors, and which host factors predispose patients to the occurrence of irAEs, potential immunological causality needs to be clarified. As such, possible explanations remain speculative. Reassuringly, in our observational study no safety alarm about the combination of influenza vaccination and immunotherapy became apparent. Until more data is available from long-term prospective studies or the observation of an increase in the incidence of irAEs due to concurrent vaccination with other non-adjuvanted vaccines – such as the polysaccharide pneumococcal vaccine – or adjuvanted vaccines – such as the conjugated pneumococcal vaccine – during immunotherapy becomes apparent, influenza vaccine appears safe. As a consequence, seasonal influenza vaccination can still be advocated in cancer patients receiving anti-PD1 immunotherapy.

## ACKNOWLEDGEMENTS

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## REFERENCES


1. Zhou TC, Sankin AI, Porcelli SA, Perlin DS, Schoenberg MP, Zang X. A review of the PD-1/PD-L1 checkpoint in bladder cancer: From mediator of immune escape to target for treatment. Urologic oncology. 2017;35(1):14-20.
2. Suarez-Almazor ME, Kim ST, Abdel-Wahab N, Diab A. Review: Immune-Related Adverse Events With Use of Checkpoint Inhibitors for Immunotherapy of Cancer. Arthritis & rheumatology (Hoboken, NJ). 2017;69(4):687-99.
3. Finn OJ. Cancer immunology. The New England journal of medicine. 2008;358(25):2704-15.
4. Davies M, Duffield EA. Safety of checkpoint inhibitors for cancer treatment: strategies for patient monitoring and management of immune-mediated adverse events. ImmunoTargets and therapy. 2017;6:51-71.
5. Baxi S, Yang A, Gennarelli RL, Khan N, Wang Z, Boyce L, et al. Immune-related adverse events for anti-PD-1 and anti-PD-L1 drugs: systematic review and meta-analysis. BMJ. 2018;360:k793.
6. Costa R, Carneiro BA, Agulnik M, Rademaker AW, Pai SG, Villaflor VM, et al. Toxicity profile of approved anti-PD-1 monoclonal antibodies in solid tumors: a systematic review and meta-analysis of randomized clinical trials. Oncotarget. 2017;8(5):8910-20.
7. Postow MA, Sidlow R, Hellmann MD. Immune-Related Adverse Events Associated with Immune Checkpoint Blockade. The New England journal of medicine. 2018;378(2):158-68.
8. Cappelli LC, Gutierrez AK, Baer AN, Albayda J, Manno RL, Haque U, et al. Inflammatory arthritis and sicca syndrome induced by nivolumab and ipilimumab. Annals of the rheumatic diseases. 2017;76(1):43-50.
9. Johnson DB, Sullivan RJ, Ott PA, Carlino MS, Khushalani NI, Ye F, et al. Ipilimumab Therapy in Patients With Advanced Melanoma and Preexisting Autoimmune Disorders. JAMA oncology. 2016;2(2):234-40.
10. Eliakim-Raz N, Vinograd I, Zalmanovici Trestioreanu A, Leibovici L, Paul M. Influenza vaccines in immunosuppressed adults with cancer. The Cochrane database of systematic reviews. 2013(10):Cd008983.
11. Boehmer LM, Waqar SN, Govindan R. Influenza vaccination in patients with cancer: an overview. Oncology (Williston Park, NY). 2010;24(12):1167-70.
12. 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. The Journal of infection. 2015;70(3):223-9.
13. Earle CC. Influenza vaccination in elderly patients with advanced colorectal cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2003;21(6):1161-6.
14. Bekkat-Berkani R, Wilkinson T, Buchy P, Dos Santos G, Stefanidis D, Devaster JM, et al. Seasonal influenza vaccination in patients with COPD: a systematic literature review. BMC pulmonary medicine. 2017;17(1):79.
15. Routy B, Le Chatelier E, Derosa L, Duong CPM, Alou MT, Daillere R, et al. Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors. Science (New York, NY). 2018;359(6371):91-7.
16. Vollaard A, Schreuder I, Slok-Raijmakers L, Opstelten W, Rimmelzwaan G, Gelderblom H. Influenza vaccination in adult patients with solid tumours treated with chemotherapy. European journal of cancer (Oxford, England : 1990). 2017;76:134-43.

17. 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. Journal for immunotherapy of cancer. 2018;6(1):40.
18. Haanen J, Carbonnel F, Robert C, Kerr KM, Peters S, Larkin J, et al. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of oncology : official journal of the European Society for Medical Oncology. 2017;28(suppl_4):iv119-iv42.
19. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). European journal of cancer (Oxford, England : 1990). 2009;45(2):228-47.
20. El Osta B, Hu F, Sadek R, Chintalapally R, Tang SC. Not all immune-checkpoint inhibitors are created equal: Meta-analysis and systematic review of immune-related adverse events in cancer trials. Critical reviews in oncology/hematology. 2017;119:1-12.
21. Guimaraes LE, Baker B, Perricone C, Shoenfeld Y. Vaccines, adjuvants and autoimmunity. Pharmacological research. 2015;100:190-209.