ONCOIMMUNOLOGY
2021, VOL. 10, NO. 1, e1886725 (7 pages)
https://doi.org/10.1080/2162402X.2021.1886725

Taylor & Francis
Taylor & Francis Group

ORIGINAL RESEARCH

OPEN ACCESS Check for updates

Improved survival without increased toxicity with influenza vaccination in cancer patients treated with checkpoint inhibitors

Antonios Valachis[a], Camilla Rosén[b], Anthoula Koliadi[c,d], Evangelos Digkas[e], Alice Gustavsson[b], Andreas Nearchou[e], and Gustav J Ullenhag[c,d]

[a]Department of Oncology, Örebro University, Örebro, Sweden; [b]School of Medical Sciences, Örebro University, Örebro, Sweden; [c]Department of Immunology, Genetics, and Pathology, Uppsala University, Uppsala, Sweden; [d]Department of Oncology, Uppsala University Hospital, Uppsala, Sweden; [e]Department of Oncology, Mälarsjukhuset, Eskilstuna, Sweden

ABSTRACT

In international guidelines, influenza vaccination is recommended to cancer patients receiving antitumor treatment. Whether this recommendation should include patients treated with the recently introduced and now widely used checkpoint inhibitors (CPIs) is unclear. The immune hyperactivation after vaccination in a patient on CPI treatment may strengthen the antitumor immunity and improve patients´ prognosis. On the other hand, there is a risk for decreased antitumor effect by the phenomenon of antigenic competition. Only results from few studies addressing survival have been reported and the results from studies on IRAEs are contradictory. We performed a multi-center retrospective cohort study at three Swedish centers in patients with metastatic cancer. All patients previously not treated with CPIs and who received monotherapy with a PD-1 or PD-L1 blocker between January 1st, 2016 until May 31st, 2019 were included. The most common type of malignancy was melanoma (47.8%) followed by non-small cell lung cancer (31.0%). Statistically significant longer PFS and OS were observed in multivariate analyses at 6-month landmark time in the vaccinated compared to the non-vaccinated group after adjustment for age, gender, comorbidity, performance status, CNS metastasis and line of treatment (p = .041 and 0.028, respectively). Furthermore, the incidence of any IRAE grade was comparable between vaccinated and non-vaccinated group (p = .85). In conclusion, the current study indicates that survival improves with influenza vaccination while not increasing the risk for side effects in cancer patients treated with checkpoint inhibitors. Hence, our results strongly support influenza vaccination in cancer patients receiving checkpoint inhibitors.

ARTICLE HISTORY
Received 15 December 2020
Revised 3 February 2021
Accepted 3 February 2021

KEYWORDS
Checkpoint inhibitor; influenza vaccination; solid cancer; progression-free survival; side effects

1. Introduction

Immunotherapy with checkpoint inhibitors (CPIs) has revolutionized cancer treatment during recent years and has become the mainstay treatment strategy for many cancer types.[1] However, several issues regarding CPIs in the real-world setting have not been adequately studied. One such issue is whether influenza vaccination should be recommended during treatment with CPIs.

Influenza vaccination is recommended by International and National Societies to all cancer patients with active cancer disease and/or receiving cancer treatment since increased infection risk is common due to cancer and cancer treatment.[2–4] Whether this recommendation should include the large and growing number of patients treated with CPIs is still a matter of discussion. Since both CPIs and influenza vaccination interfere with the immune system, there is a theoretical risk for interaction between the two approaches.[5] The immune activation by CPIs may be further enhanced by vaccination, leading to a higher risk for immune-related adverse events (IRAEs). Furthermore, the phenomenon of antigenic competition may decrease the antitumor effect.[5] On the other hand, the vaccine induced immune hyperactivation, in a patient who already, due to CPI treatment, has an activated immune system, may strengthen the antitumor immunity and improve patients´ prognosis.

Recent small prospective studies suggest that immunogenicity after influenza vaccination is higher in patients treated with CPIs compared to either healthy individuals or patients treated with chemotherapy.[6–8] However, the clinically relevant question whether influenza vaccination significantly interacts with CPIs in terms of treatment efficacy and IRAEs remains unanswered.

So far, there is little and conflicting evidence on the potentially increased risk for IRAEs through interaction between influenza vaccination and treatment with CPIs.[6,9–12] Regarding treatment efficacy, current evidence is also sparse but it indicates a potential improved survival in cancer patients who received influenza vaccination during treatment with checkpoint inhibitors.[9,10,13,14] However, none of the current studies managed to deal with immortal-time bias (patients in the vaccination group have an "immortal" time-period until vaccination) leading to a potential overestimation of survival benefit.

CONTACT Antonios Valachis antonios.valachis@oru.se Department of Oncology, Örebro University, Örebro SE 70182, Sweden.
Supplemental data for this article can be accessed on the publisher's website.

Considering the few and overall small studies reported and their contradictory results, and the high risk of immortal-time bias in prior analyses, further studies are necessary to address the potential interaction between treatment with CPIs and influenza vaccination. We, therefore, aimed to investigate the possible impact of influenza vaccination on the antitumoral efficacy and the rate of IRAEs in patients with metastatic cancer treated with CPIs. Survival outcomes (PFS and OS) were assessed in all patients and suitable methods to mitigate the risk for immortal-time bias were applied.

2. Patients and methods

2.1. Study cohort

We performed a multi-center retrospective cohort study including three Regions (Sörmland, Uppsala län, Örebro län) in Sweden. The study was approved by the Regional Ethics Committee (-2019–02469). All patients who received monotherapy with a PD-1 or PD-L1 blocker for metastatic solid malignancy between January 1st, 2016 until May 31st, 2019 were included.

Hence, we excluded patients who received the CPI as adjuvant therapy and those previously treated with CPIs.

2.2. Data collection

From the electronic medical records (EMRs), the following data were collected: age at diagnosis, gender, comorbidities expressed as Charlson Comorbidity Index (CCI), type of cancer, primary treatment at diagnosis, age at diagnosis of non-curative cancer, metastatic sites, CPI initiation date, performance status (WHO classification) at CPI initiation, number of previous lines of treatment, best treatment response on CPI, date of disease progression, immune-related adverse events (date, type, grade, outcome), influenza vaccination status, date of death, and cause of death.

Influenza vaccination status was captured through hospital-based EMRs but also from EMRs in primary care.

2.3. Definitions and outcomes

Patients were considered vaccinated if they had received influenza vaccination during treatment with CPI or up to 60 days prior to treatment initiation.

Progression-free survival was defined as the time from CPI initiation until proven disease progression through clinical manifestation or radiologic findings or death due to any cause. Overall survival (OS) was defined as the time from CPI initiation until patient death due to any cause.

Immune-related toxicity was defined using the Common Terminology Criteria for Adverse Events (CTCAE), version 4.03.[15] Toxicity grades 1–2 were considered mild IRAEs whereas toxicity grades 3–5 were considered serious IRAEs. Symptoms of IRAEs up to 6 months after treatment end date were taken into calculation.

2.4. Statistical methods

Categorical variables were summarized using numbers and percentages whereas median and range were used for continuous variables. Bivariate analyses were performed using the chi-square test for categorical variables and the Mann-Whitney U test for continuous variables (all continuous variables were non-normally distributed).

For time-to-event outcomes (PFS and OS), two different approaches to mitigate immortal-time bias were used. The primary analysis of time-to-event outcomes was performed with the landmark analysis in two different landmark times: at month 6 which was the time period between CPI initiation and influenza vaccination for at least 80% of patients and at month 12 which was the longest time between CPI-initiation and vaccination within the study cohort. Kaplan-Meier curves were constructed from the two landmarks times and onwards and log-rank test was used for comparison of the vaccinated vs. non-vaccinated groups. Cox regression hazards models in the two landmark times were used to investigate the association of vaccination status with PFS and OS, respectively, after adjustment for prior, well-established factors that could influence outcomes (age, gender, CNS metastasis, performance status, CCI, and line of treatment). A sensitivity analysis was performed using time-dependent Cox regression models for PFS and OS as an additional approach to mitigate immortal-time bias.

To minimize the risk of selection bias in the analysis of IRAEs (patients without IRAEs may be more likely to continue therapy and receive vaccination), only patients who received influenza vaccination within 2 months before or after CPI initiation were compared with non influenza vaccinated patients.

All the analyses were performed in SPSS v.23.0. All p-values were two-sided and a p-value <0.05 was considered statistically significant.

2.5. Ethical approval

The study has been approved by the Swedish Ethical Review Authority, Dnr 2019–02469. Considering the retrospective nature of the study, the Ethical Review Authority waive the requirement to obtain any informed consent.

3. Results

3.1. Study cohort

In total, 329 patients treated with CPIs during the study period were identified. Of those, 303 patients met the inclusion criteria and were included in the analyses. A flowchart diagram of patient selection is shown in Figure 1.

The most common type of malignancy within the study cohort was melanoma (143 patients; 47.8%) followed by non-small cell lung cancer (94 patients; 31.0%). Within the study cohort, 209 patients (69.0%) received nivolumab, 86 (28.4%) pembrolizumab, and 8 (2.6%) atezolizumab (Table 1).

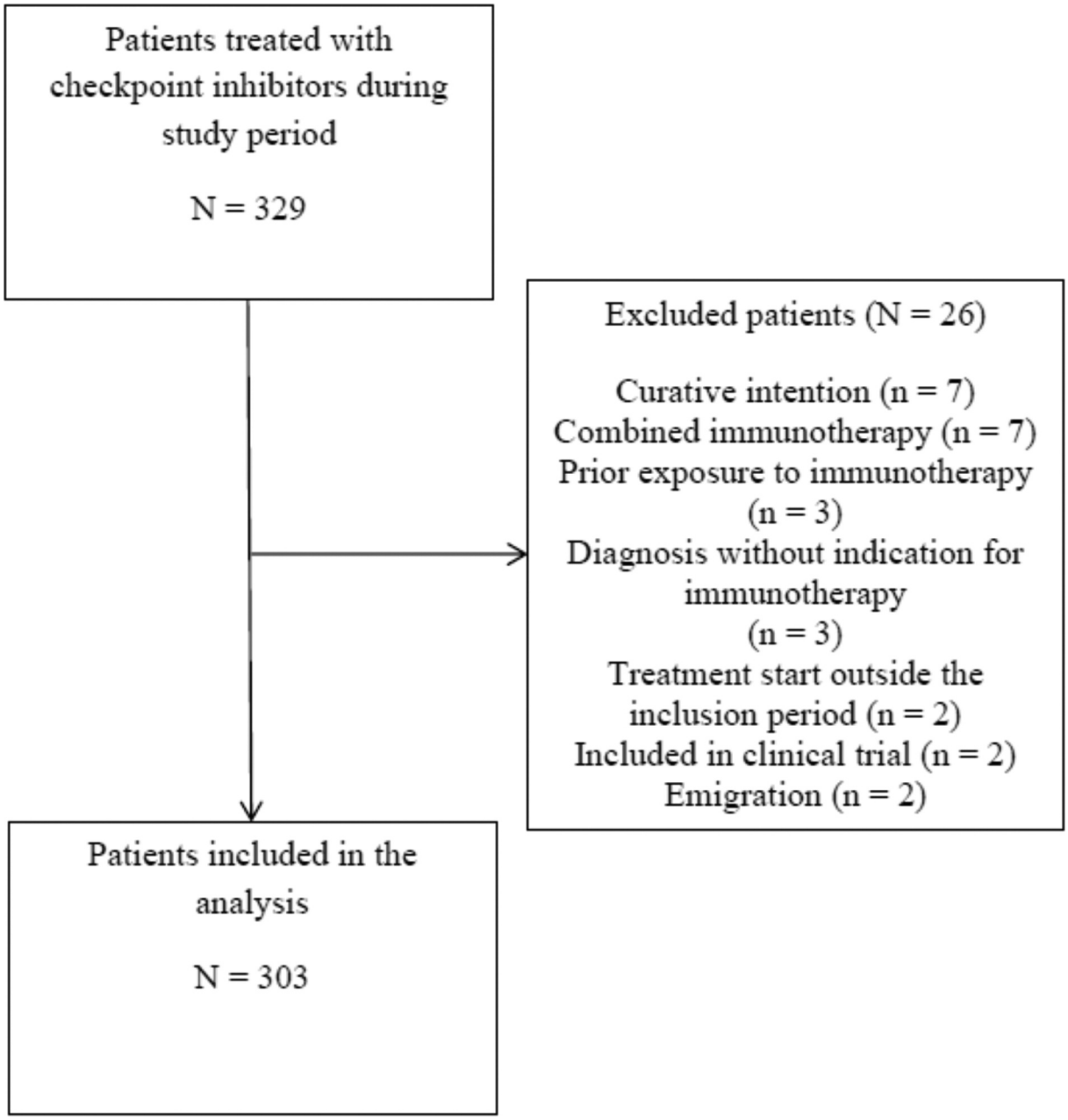

Figure 1. Flowchart diagram of patient selection.

3.2. Influenza vaccination in study cohort

Sixty-seven patients (22.1%) were vaccinated against influenza during the study period. The time from CPI initiation (time 0) until vaccine administration ranged between −2 months (up to 2 months prior to CPI initiation) to 12 months with a median of zero months (vaccine administration within two weeks from CPI administration).

The baseline characteristics between the non-vaccinated and vaccinated groups were comparable except from CCI where patients with CCI ≥ 3 had a higher rate of influenza vaccination (Table 1). This difference remained statistically significant when the age-not CCI, namely the CCI without adjusted for age, was used (10.4% for CCI 0, 19.2% for CCI 1, 15.8% for CCI 2, 50% for CCI ≥ 3; p-value <0.001).

The median follow-up time for the study cohort was 15 months (range: 1–52 months).

3.3. Landmark analyses at 6 months

At 6-month landmark time, 225 patients were eligible for analysis including 57 patients in the vaccinated group and 168 patients in the non-vaccinated group.

A statistically significant longer PFS was observed in the vaccinated group compared to the non-vaccinated (log-rank test p-value = 0.006; Figure 2(a)).

Patients in the vaccinated group had a statistically significant longer OS than patients in the non-vaccinated group (log-rank test p-value = 0.012; Figure 2(b)). No patient died due to influenza infection.

Table 1. Patient characteristics in study cohort.

	Whole cohort (n = 303)	Non-vaccinated (n = 236)	Vaccinated (n = 67)	P-value
Age at diagnosis in years, median (IQR)	67 (13)	67 (13)	70 (15)	0.373
Gender, n (%)	171 (56.4)	133 (56.4)	38 (56.7)	0.958
Male	132	103	29	
Female	(43.6)	(43.6)	(43.3)	
Type of malignancy, n (%)	143 (47.2)	116 (49.2)	27 (40.3)	0.428
Melanoma	94	69 (29.2)	25	
Non small cell lung cancer	(31.0)	30 (12.7)	(37.3)	
Renal cell carcinoma	39	11 (4.7)	9 (13.4)	
Urothelial cancer	(12.9)	10 (4.2)	5 (7.5)	
Head & neck cancer	16 (5.3)		1 (1.5)	
	11 (3.6)			
Visceral metastasis, n (%)	222 (73.3)	172 (72.9)	50 (74.6)	0.776
Yes	81	64 (27.1)	17	
No	(26.7)		(25.4)	
CNS metastasis, n (%)	33 (10.9)	30 (12.7)	3 (4.5)	0.073
Yes	270	206	64	
No	(89.1)	(87.3)	(95.5)	
Type of CPI	209 (69.0)	163 (69.1)	46 (68.7)	0.780
Nivolumab	86	66 (28.0)	20	
Pembrolizumab	(28.4)	7 (3.0)	(29.9)	
Atezolizumab	8 (2.6)		1 (1.5)	
Performance status at CPI	245 (80.9)	188 (79.7)	57 (85.1)	0.320
initiation	58	48 (20.3)	10	
0–1	(19.1)		(14.9)	
2–3				
Charlson Comorbidity Index	31 (10.2)	29 (12.3)	2 (3.0)	<0.001
0	32	27 (11.4)	5 (7.5)	
1	(10.6)	62 (26.3)	6 (9.0)	
2	68	118	54	
≥3	(22.4)	(50.0)	(80.6)	
	172			
	(56.8)			
Line of treatment (for CPI)	123 (40.6)	96 (40.7)	27 (40.9)	0.973
1	179	140	39	
≥2	(59.1)	(59.3)	(59.1)	

Abbreviations: IQR, interquartile range; CNS, central nervous system; CPI, checkpoint inhibitors.

Multivariate analysis for PFS showed that influenza vaccination was associated with better PFS (HR = 0.63, 95% CI: 0.41–0.98, p-value = 0.041; Supplementary Table 1) after adjustment for age, gender, CCI, performance status, CNS metastasis, and line of treatment.

Similarly, in multivariate analysis (adjusted for age, gender, CCI, performance status, CNS metastasis, line of treatment) for OS, we found a statistically significant difference of OS in favor of the vaccinated group (HR = 0.53, 95% CI = 0.30–0.93, p-value = 0.028; Supplementary Table 2).

3.4. Landmark analysis at 12 months

At 12-months landmark time, 178 patients (50 in the vaccinated group; 128 in the non-vaccinated group) were eligible for analysis.

The vaccinated group had a numerical, but statistically non-significant, longer PFS (log-rank test p-value = 0.093; Figure 2(c)) and OS (log rank test p-value = 0.060; Figure 2(d)) compared to the non-vaccinated group. No patient died due to influenza infection.

Multivariate analyses at 12-month landmark time did not show a statistically significant association between vaccination and either PFS (HR = 0.71, 95% CI: 0.43–1.17, p-value = 0.176; Supplementary Table 3) or OS (HR = 0.62, 95% CI: 0.30–1.28, p-value = 0.194; Supplementary Table 4).

3.5. Sensitivity analysis

A sensitivity analysis for each outcome (PFS, OS) was performed using time-dependent Cox regression analysis as an approach to minimize immortal time bias. The same covariates that were used to adjust the multivariate models in the landmark analyses were also used in the time-dependent Cox regression models.

Patients in the vaccinated group had a statistically significant better PFS (HR = 0.68, 95% CI: 0.46–0.96, p-value = 0.029) and OS (HR = 0.62, 95% CI: 0.40–0.96, p-value = 0.031) in the sensitivity analysis compared to patients in the non-vaccinated group.

3.6. IRAEs and influenza vaccination

A detailed description on the type of IRAE and outcome is presented in Table 2.

Twenty-nine of 67 patients in the vaccinated group were available for the analysis of IRAEs based on the time of vaccination in relation to CPI initiation in order to mitigate the risk for selection bias. The incidence of any IRAE grade was comparable between non-vaccinated and vaccinated group (43% vs. 44.8%, p-value = 0.850). Considering grade 3–4 IRAEs, the incidence between the groups was also comparable (15.7% for non-vaccinated vs. 13.8% for vaccinated group, p-value = 0.932).

4. Discussion

In our study cohort of over 300 patients with metastatic cancer treated with CPIs, influenza vaccination was associated with prolonged survival after applying two different approaches to avoid immortal-time bias. The main survival analysis at 6-month landmark time and the time-dependent Cox model showed a clear benefit in survival for the vaccinated group. However, the survival analysis at 12-month landmark time did not reveal statistically significant better survival for the vaccinated compared to the non-vaccinated group. Of note, our study could not find any increased risk for IRAEs after influenza vaccination where only patients vaccinated within 2 months before or after initiation of CPI treatment were included to avoid the risk for selection bias.

A potential mechanism that could explain the improved survival in vaccination group in our study is the hypothesis that immune hyperactivation after vaccination may enhance antitumor immunity. Recently, intra-tumoral injection of influenza vaccine showed to reduce tumor growth in a mouse model through converting the immunologically "cold" tumor microenvironments to "hot".[16]

The current evidence on the potential impact of influenza vaccination on survival in patients treated with CPIs is limited to a few retrospective studies.[9,10,13,14] In non-small cell lung cancer patients treated with nivolumab, no difference in treatment efficacy was found between vaccinated and non-vaccinated patients.[9] However, Bersanelli et al.

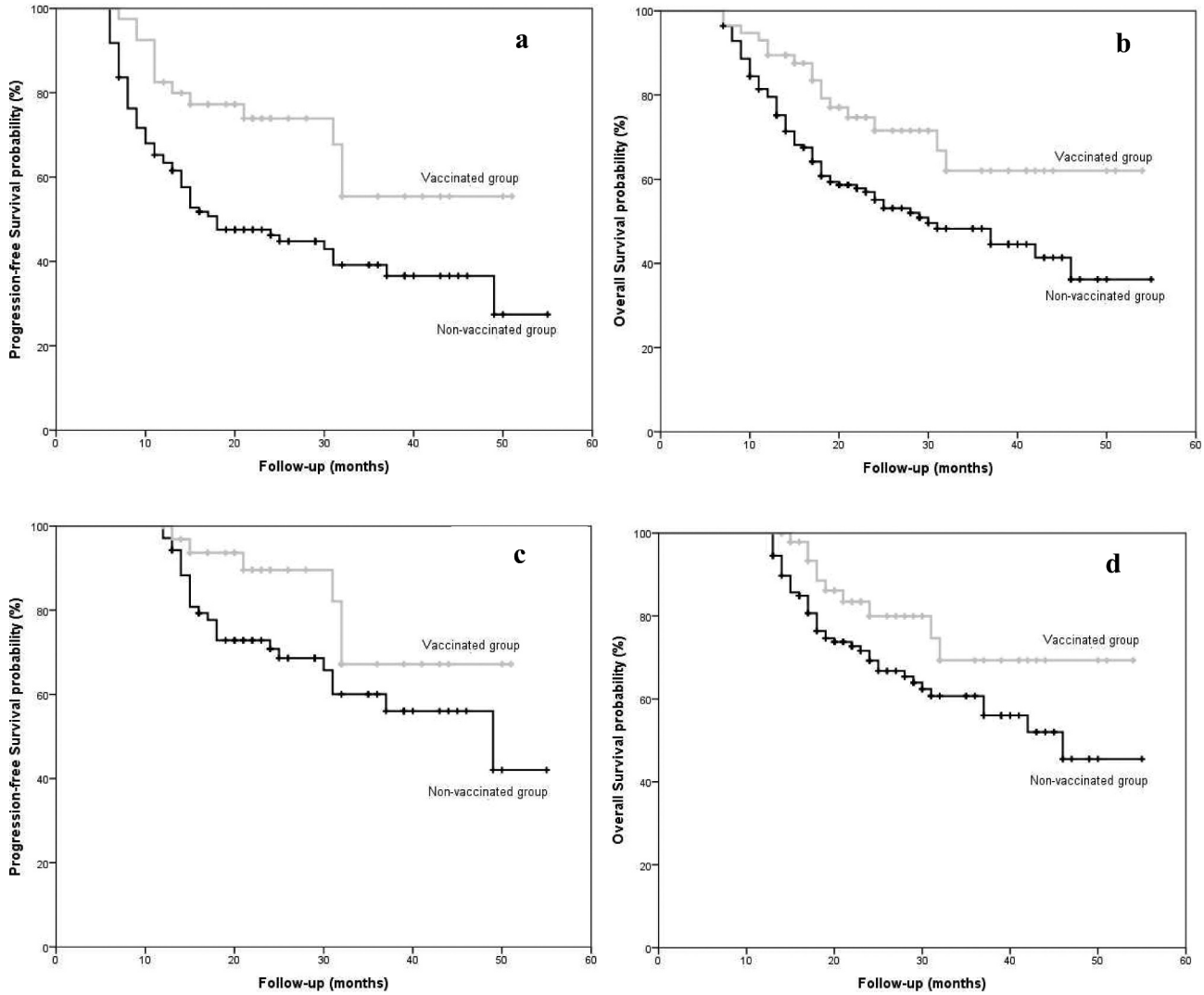

Figure 2. Kaplan-Meier curves for progression-free and overall survival comparing vaccinated and non-vaccinated groups in two different landmark times: (a) progression-free survival at 6-month landmark time; (b) overall survival at 6-month landmark time; (c) progression-free survival at 12-month landmark time; (d) overall survival at 12-month landmark time.

found an improved survival in favor of the vaccinated group in patients with metastatic cancer treated with CPIs.[13] Similarly, two retrospective studies, presented only as meeting abstracts, found a survival trend in favor of vaccinated patients treated with CPIs.[10,14] The current evidence is, however, prone to immortal-time bias, namely patients in the vaccinated group have an "immortal" time period from CPI initiation until vaccine administration that can overestimate a potential survival benefit from the vaccination. None of the available studies have described if they dealt with immortal-time bias in their analyses. On the other hand, we used two different statistical approaches to assure that the survival benefit observed in our study cohort is not influenced by immortal-time bias.[17,18] Although the main landmark analysis at 6-months (timepoint where at least 80% of patients in vaccinated group were vaccinated) and time-dependent Cox analysis showed similar results of improved survival in the vaccinated group, the landmark analysis at 12-months (timepoint where all patients in vaccinated group were vaccinated) showed a statistically non-significant survival difference. The lack of statistical significance in the 12-month landmark time may be explained by the smaller number of patients in this analysis compared to 6-month landmark time and the time-dependent Cox analysis, resulting in lower statistical power. Anyhow, these approaches make our results more reliable as compared to previous studies.

Considering IRAE risk after influenza vaccination, some early evidence suggested an increased risk for IRAEs after influenza vaccination[6] but recent studies could not confirm this observation.[11,12] The analysis of IRAEs in relation to influenza vaccination in patients treated with CPIs is prone to selection bias, namely patients without side effects are more likely to continue with CPIs and receive vaccination, which can lead to a false lower rate of IRAEs in vaccinated patients. To deal with selection bias, we analyzed IRAEs in patients who received vaccination within 2 months before or after CPI treatment initiation and found no difference compared to patients treated with CPIs without receiving vaccination. Two prior studies also tried to deal with selection bias, either

Table 2. Immune-related adverse events (IRAEs) between influenza vaccinated (patients with vaccination within 2 months before or after checkpoint inhibitor initiation) and non-vaccinated patients.

	Non-vaccinated group (n = 236)	Vaccinated group (n = 29)	P-value
IRAEs	101 (43.0)	13 (44.8)	0.850
Any grade	74 (31.5)	10 (34.5)	0.932
Grade 1–2	37 (15.7)	4 (13.8)	
Grade 3–4			
Type of IRAE	27 (11.5)	2 (6.9)	0.338
Endocrine	25 (10.6)	1 (3.4)	
Skin toxicity	11 (4.7)	3 (10.3)	
Rheumatic	13 (5.5)	0 (0.0)	
Hepatitis	8 (3.4)	2 (6.9)	
Colitis	10 (4.3)	1 (3.4)	
Pneumonitis	4 (1.7)	2 (6.9)	
Neurologic	3 (1.3)	1 (3.4)	
Renal toxicity	10 (4.3)	2 (6.9)	
Other			
Outcome of IRAE	66 (48.2)	7 (42.9)	0.480
Resolved without sequelae	32 (23.4)	6 (42.9)	
Resolved with minor sequelae	6 (4.4)	1 (7.1)	
Resolved with major sequelae	4 (2.9)	0 (0.0)	
Worsening	2 (1.5)	0 (0.0)	
Death due to IRAE			

through subgroup analysis of patients receiving vaccination within 65 days from CPI initiation[12] or through adjustment of IRAE risk with number of treatment cycles, [11] and both found similar results as we did.

In our study cohort, we observed an association between vaccination rate and CCI that seemed to be present even when the age-not CCI was used. This trend of higher vaccination rate in patients with more comorbid conditions has been previously described[11] and might reflect the healthcare providers' practice to encourage vaccination among patients with comorbidities and/or an increased vaccine acceptance among those patients.

The current study has some limitations. First, the retrospective study design is inherent to selection bias and immortal-time bias which we tried to adjust for as described above. The risk for selection biases was also limited by not including patients receiving CPIs in clinical studies. Second, in this real-world study, we included patients with different types of metastatic disease. We found, however, no difference in vaccination pattern among different cancer types but a different effect of combining CPI and vaccination in patients with different cancer types cannot be completely ruled out. Furthermore, a risk for misclassification of patients within the non-vaccinated group cannot be excluded because of the lack of information about vaccinations administered at private outpatient clinics. Though, this risk is considered small since the private health care sector in the uptake areas for this study as in Sweden in general is small.[19] In addition, a true survival difference between vaccinated and non-vaccinated is more difficult to detect if some vaccinated patients are falsely classified as non-vaccinated which strengthens our positive survival results. Finally, the median follow-up of study cohort is relatively short with risk to miss late IRAEs. However, most IRAEs are presented within the first months from the initiation of CPIs.[20]

In conclusion, the current study indicates that survival in metastatic cancer patients treated with CPIs in monotherapy improves with influenza vaccination while not increasing the risk for side effects. The study is the largest reported on IRAEs in this setting and the first taking the risk of immortal-time bias into account. Our results strongly support influenza vaccination in patients with metastatic cancer going to receive or receiving CPIs. A prospective evaluation of the synergistic effect of influenza vaccination with CPI treatment as a potential treatment strategy is justified. It is also important to investigate the role of influenza vaccination in patients treated with combination immunotherapy and in patients receiving CPI in the adjuvant setting. Furthermore, studies addressing whether other vaccines than influenza interact differently with immunotherapy are warranted.

Disclosure statement

None of the authors has any potential financial conflict of interest related to this manuscript.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

ORCID

Antonios Valachis http://orcid.org/0000-0001-6059-0194

"Data accessibility" statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

References

1. Hargadon KM, Johnson CE, Williams CJ. Immune checkpoint blockade therapy for cancer: an overview of FDA-approved immune checkpoint inhibitors. Int Immunopharmacol. 2018;62:29–39.
2. Rubin LG, Levin MJ, Ljungman P, Davies EG, Avery R, Tomblyn M, Bousvaros A, Dhanireddy S, Sung L, Keyserling H, et al. IDSA clinical practice guidelines for vaccination in immunocompromised host. Clin Infect Dis. 2013;58(2014):309–318. doi:10.1093/cid/cit816.
3. Pedrazolli P, Baldanti F, Donatelli I, Castrucci MR, Puglisi F, Silvestris N, Cinieri S. Italian Society of Medical Oncology. Vaccination of seasonal influenza in patients with cancer: recommendations of the Italian Society of Medical Oncology (AIMO). Ann Oncol. 2014;25:1243–1247. doi:10.1093/annonc/mdu114.
4. Recommendations of the public health agency of Sweden about influenza vaccination. [accessed 2020 June 27]. https://www.folkhalsomyndigheten.se/smittskydd-beredskap/vaccinationer/vaccin er-a-o/influensa/.
5. Blobel NJ, Ramirez-Valdez A, Ishizuka AS, Lynn GM, Seder RA. Antigenic competition affects the magnitude and breadth of CD8 T cell immunity following immunization with a nanoparticle neoantigen cancer vaccine. J Immunol. 2017;198:Supplement 7320.
6. Läubli H, Balmelli C, Kaufmann L, Stanczak M, Syedbasha M, Vogt D, Hertig A, Müller B, Gautschi O, Stenner F, 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. doi:10.1186/s40425-018-0353-7.

7. Keam B, Kang CK, Jun KI, Moon SM, Suh KJ, Lee DW, Ock CY, Kim M, Choi Y, Lim Y, et al. Immunogenicity of influenza vaccination in patients with cancer receiving immune checkpoint inhibitor. Clin Infect Dis. 2020;71:422–425. doi:10.1093/cid/ciz1092.
8. Bayle A, Khettab M, Lucibello F, Chamseddine AN, Goldschmidt V, Perret A, Ropert S, Scotté F, Loulergue P, Mir O. Immunogenicity and safety of influenza vaccination in cancer patients receiving checkpoint inhibitors targeting PD-1 or PD-L1. Ann Oncol. 2020;31:959–961. doi:10.1016/j.annonc.2020.03.290.
9. Wijn DH, Groeneveld GH, Vollaard AM, Muller M, Wallinga J, Gelderblom H, Smit EF. Influenza vaccination in patients with lung cancer receiving anti-programmed death receptor 1 immunotherapy does not induce immune-related adverse events. Eur J Cancer. 2018;104:182–187. doi:10.1016/j.ejca.2018.09.012.
10. Schenk EL. Clinical outcomes of patients on check point inhibitor therapy who receive routine vaccinations. J Clin Oncol. 2017;35:e14597. doi:10.1200/JCO.2017.35.15_suppl.e14597.
11. Failing JJ, Ho TP, Yadav S, Majithia N, Riaz IB, Shin JY, Schenk EL, Xie H. Safety of influenza vaccine in patients with cancer receiving pembrolizumab. JCO Oncol Pract. 2020;16:JOP1900495. doi:10.1200/JOP.19.00495.
12. 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;70:193–199. doi:10.1093/cid/ciz202.
13. Bersanelli M, Buti S, Banna GL, De Giorgi U, Cortellini A, Rebuzzi SE, Tiseo M, Fornarini G, Mazzoni F, Panni S, et al. Impact of influenza syndrome and flu vaccine on survival of cancer patients during immunotherapy in the INVIDIa study. Immunotherapy. 2020;12:151–159. doi:10.2217/imt-2019-0180.
14. Gopalakrishnan R, Buckner Johnson D, York S, Neuss MN, Osterman TJ, Chism DD, Ancell KK, Mayer IA, Abramson VG, Levy MA, et al. Impact of the influenza vaccination on cancer patients undergoing therapy with immune checkpoint inhibitors. J Clin Oncol. 2018;36:3053. doi:10.1200/JCO.2018.36.15_suppl.3053.
15. National Cancer Institute. Common terminology criteria for adverse events (CTCAE) Version 4.03. [accessed 2020 June 28]. https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf
16. Newman JH, Chesson CB, Herzog NL, Bommareddy PK, Aspromonte SM, Pepe R, Estupinian R, Aboelatta MM, Buddhadev S, Tarabichi S, et al. Intratumoral injection of the seasonal flu shot converts immunologically cold tumors to hot and serves as an immunotherapy for cancer. Proc Natl Acad Sci U S A. 2020;117:1119–1128. doi:10.1073/pnas.1904022116.
17. Gleiss A, Oberbauer R, Heinze G. An unjustified benefit: immortal time bias in the analysis of time-dependent events. Transpl Int. 2018;31:125–130.
18. Harrison SM, Wei MY, Lamerato LE, Petrie JG, Toth Martin E. Multimorbidity is associated with uptake of influenza vaccination. Vaccine. 2018;36:3635–3640. doi:10.1016/j.vaccine.2018.05.021.
19. Stig K, Paulsson Lütz I. The Nordic reference group. Financing of health care in the Nordic countries. Copenhagen: Nordic Medico Statistical Committee; 2013.
20. Martins F, Sofiya L, Sykiotis GP, Lamine F, Maillard M, Fraga M, Shabafrouz K, Ribi C, Cairoli A, Guex-Crosier Y, et al. Adverse effects of immune-checkpoint inhibitors: epidemiology, management and surveillance. Nat Rev Clin Oncol. 2019;16:563–580. doi:10.1038/s41571-019-0218-0.