INfluenza Vaccine Indication During therapy with Immune checkpoint inhibitors: a transversal challenge. The INVIDIa study

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Aim: Considering the unmet need for the counseling of cancer patients treated with immune checkpoint inhibitors (CKI) about influenza vaccination, an explorative study was planned to assess flu vaccine efficacy in this population. Methods: INVIDIa was a retrospective, multicenter study, enrolling consecutive advanced cancer outpatients receiving CKI during the influenza season 2016–2017. Results: Of 300 patients, 79 received flu vaccine. The incidence of influenza syndrome was 24.1% among vaccinated, versus 11.8% of controls; odds ratio: 2.4; 95% CI: 1.23–4.59; p = 0.009. The clinical ineffectiveness of vaccine was more pronounced among elderly: 37.8% among vaccinated patients, versus 6.1% of unvaccinated, odds ratio: 9.28; 95% CI: 2.77–31.14; p < 0.0001. Conclusion: Although influenza vaccine may be clinically ineffective in advanced cancer patients receiving CKI, it seems not to negatively impact the efficacy of anticancer therapy.

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Keywords: immune checkpoint inhibitors ● influenza syndrome ● influenza vaccine
Background
Prevention of infection is crucial for individuals with impaired immunity. Viral infections in cancer patients often result in high morbidity and mortality rates, the latter reaching 9% for influenza syndrome (IS) [1,2]. Because of tumor- and treatment-induced immunosuppression, live vaccines are not used, while split vaccines are permitted and often recommended for this population [3–5]. However, the greater the degree of immunosuppression, the less likely the patient is to respond to vaccine immunization [1]. Some evidence in favor of serological response to influenza vaccination in high-risk patients with proliferative diseases has been provided [6,7], but it remains unclear how much this response protects them from flu infection, due to the lack of morbidity measures [8]. The few available data about immunocompromised patients have been summarized in a meta-analysis, showing significantly lower odds of influenza-like illness for vaccinated individuals [9].

Nevertheless, immunogenicity could vary widely basing on different tumor types and treatment regimens. It is generally assumed that the advanced cancer patient, mainly treated with chemotherapy, is a fragile and immunocompromised subject, who, regardless of age, must be included in the vaccination strategy. Influenza vaccine is recommended in all cancer patients, especially those with lung cancer, considering their susceptibility and high mortality from infectious respiratory diseases [3–5,10].

In the last years, the new immunotherapy with immune checkpoint inhibitors (CKI) revolutionized the systemic treatment of advanced solid tumors such as melanoma, lung cancer, renal carcinoma, urothelial cancers, and head and neck carcinoma [11]. This new oncologic population has not been specifically studied for its susceptibility to infections. The goal of the new immunotherapy is to restore the cellular immunocompetence. It is therefore plausible that the patient underwent treatment with CKI could be more immunocompetent than the average cancer patient.

It is only based on the drugs characteristics that flu vaccine has been considered as potentially safe in patients treated with CKI. The Phase II study CA184–004, providing the only formal proof of humoral efficacy of vaccines during CKI immunotherapy, demonstrated humoral responses to influenza vaccine in melanoma patients treated with ipilimumab [12]. Nevertheless, no data have been provided to date about the clinical efficacy of flu vaccine during CKI, nor about its potential impact on the efficacy of anticancer immunotherapy. A small case–control study, very recently published, suggested that the seasonal influenza vaccination may increase the rate of serious immune-related adverse events (irAEs) from CKI [13]. Interestingly, CKI-treated patients described in this report had greater and more rapid humoral response compared with that of vaccinated healthy controls. Such data support the hypothesis that CKI-treated patients could be more immunocompetent, since immunotherapy enhances cellular and humoral immunity. Influenza vaccine in such subjects can result in an overwhelming activation of the immune system, potentially amplifying irAEs of CKI [12,13].

The effect of introducing a new antigen in the immune system of individuals treated with CKI is unknown. Viral antigens, according to the concept of the ‘foreignness’, are much more immunogenic than tumor antigens [14–19]; thus, they could deviate T-cell response induced by CKI, potentially weakening the antitumor response in favor of the antiviral reaction. The effectiveness of anticancer treatment might be consequently undermined, especially if vaccination occurs closer to the start of CKI therapy, when the immune response has not yet been established.

Considering the transversal unmet need for the counseling of CKI-treated cancer outpatients about flu vaccination, an explorative study was planned, to assess the efficacy of influenza vaccine in this population, its potential impact on the severity and mortality of IS and on the outcome of anticancer immunotherapy.

Patients & methods
INVIDIa was a retrospective, observational, multicenter, explorative study, conducted at the Medical Oncology Units from 21 Italian centers, approved by the respective Local Ethical Committees. Records of consecutive advanced cancer outpatients receiving treatment with CKI during the Italian influenza vaccinal season 2016–2017, namely from 1 November 2016 to 30 May 2017, were collected in an anonymized database. Any primary tumor and any systemic treatment with anti-PD-1, anti-PD-L1 or anti-CTLA-4 antibodies, with at least one administration in the observation period, were allowed. Detailed information regarding influenza vaccination, IS occurrence and treatment with CKI was retrospectively investigated during the Italian flu season, from 1 November 2016 to 30 May 2017, also contacting the primary care physician of each patient. Patients lacking availability of exhaustive data about influenza vaccine administration or IS development were excluded.
Flu vaccine indication during cancer immunotherapy

Research Article

IS, according to the Italian Ministry of Health, was defined as illness of likely viral origin, with acute onset, characterized by fever ≥ 38°C and the presence of at least one respiratory symptom (cough, dyspnea or rhinorrhea) and general symptoms (headache, myalgias, bone or joint pains) [20].

With the aim of assessing the efficacy of influenza vaccine in this population, by comparing the morbidity of IS among vaccinated and unvaccinated patients, the primary end point of the study was the incidence of IS.

Several secondary end points were investigated. Severity and lethality of IS were evaluated in terms of flu-related death rate (defined as the proportion of patients which death was attributable to IS or its complications); flu-relapse rate (the proportion of patients experiencing at least a recurrence of the flu episode); need for hospitalization due to flu illness; need for intravenous therapy in day-hospital regimen due to flu-related symptoms; incidence of documented bacterial superinfections; and flu-syndrome duration. The impact of influenza vaccine and IS on the outcome of patients was investigated in terms of objective response rate (ORR) obtained with CKI (defined as the rate of complete and partial responses assessed by RECIST 1.1 [21]); disease control rate (DCR, defined as the rate of stable diseases, partial and complete responses); time to treatment failure (TTF, defined by the time from CKI treatment initiation to permanent discontinuation for any reason); and median overall survival (mOS, defined from therapy starting to death for any reason). Follow-up for overall survival (OS) is still ongoing; only preliminary survival data will be reported herein.

Preplanned subgroup analyses

Subgroup analyses were preplanned for lung cancer patients and for elderly, using as prespecified cutoff the median age of the vaccinated subgroup at the time of flu vaccine administration. Age for the control group was calculated at the start of the observation period.

Hypothesizing higher risk of interaction with immunotherapy when flu vaccine was administered in its early phase, further subgroup analyses for ORR, DCR, TTF and OS were planned in the selected population of patients initiating CKI therapy closer to the vaccinal season, namely starting treatment after the 1 August 2016.

Statistical analyses

Demographic variables were reported using descriptive statistics. Median values were associated with their interquartile range (IQR) or 95% CI and compared using the Mann–Whitney t-test. \( \chi^2 \) test was used to evaluate the association between categorical variables. Survival curves were estimated with the Kaplan–Meier method, and the outcomes in groups were compared using the log-rank test. Cox proportional hazard model was used to estimate hazard ratio and 95% CI for each factor and in a multivariate analysis, including all evaluable parameters, using a forward stepwise selection method.

Results

Overall INVIDIa study population

Characteristics of patients

The INVIDIa study enrolled 300 advanced cancer outpatients; their characteristics are reported in Table 1. mOS (Supplementary Figure 1A) was not reached at the median follow-up of 12.2 months (95% CI: 11.2–13.3; 232 censored). Immunotherapy was still ongoing for 149 patients at the data cutoff; median TTF (mTTF) was of 11.7 months (95% CI: 9.0–14.5). Response to treatment was significantly related to OS (p < 0.0001, Supplementary Figure 1B).

Overall, 79 patients received influenza vaccine (26.3%), as classical intramuscular injectable flu shot, with trivalent (two type A viruses, H1N1 and H3N2, and one type B virus, B/Br) or quadrivalent (adding a type B virus, B/Phuket) inactivated virus vaccine (split vaccine), according to the National and International recommendations [22,23]. The remaining 221 patients did not receive flu vaccination, constituting the control group.

Of the 79 vaccinated patients, 31 received the flu shot before starting immunotherapy, with median time interval of 2.6 months (IQR = 1.0–4.5), while 48 patients were vaccinated after prior immunotherapy initiation, with median time interval of 8.1 months (IQR = 3.4–10.0). The patient population that started CKI treatment closer to the vaccinal season (namely after the 1 August 2016) was of 184 cases, with median follow-up of 8.5 months (95% CI: 7.2–9.7). Their mOS was of 15.3 months (95% CI: 10.3–20.3; 131 censored); mTTF was of 5 months (95% CI: 3.3–6.6; 80 censored). Of the 45 patients with occurrence of IS during the study observation period, 40 developed the illness after immunotherapy initiation, with median time interval of 7.3 months (IQR = 2.4–12.8),
Table 1. Characteristics of the INVIDIa patient population.

<table>
<thead>
<tr>
<th>Clinical characteristic</th>
<th>Number of patients (%) overall population</th>
<th>Number of patients (%) vaccinated group</th>
<th>Number of patients (%) control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>207 (69%)</td>
<td>59 (74.7%)</td>
<td>148 (67%)</td>
</tr>
<tr>
<td>Female</td>
<td>93 (31%)</td>
<td>20 (25.3%)</td>
<td>73 (33%)</td>
</tr>
<tr>
<td>Primary tumor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-small-cell lung cancer</td>
<td>103 (34.3%)</td>
<td>33 (41.8%)</td>
<td>70 (31.7%)</td>
</tr>
<tr>
<td>Renal cell carcinoma</td>
<td>112 (37.3%)</td>
<td>24 (30.4%)</td>
<td>88 (39.8%)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>55 (18.3%)</td>
<td>13 (16.4%)</td>
<td>42 (19%)</td>
</tr>
<tr>
<td>Other†</td>
<td>30 (10%)</td>
<td>9 (11.4%)</td>
<td>21 (9.5%)</td>
</tr>
<tr>
<td>Treatment line</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I line</td>
<td>43 (14.3%)</td>
<td>10 (12.7%)</td>
<td>33 (14.9%)</td>
</tr>
<tr>
<td>II line</td>
<td>124 (41.3%)</td>
<td>38 (48.1%)</td>
<td>86 (38.9%)</td>
</tr>
<tr>
<td>III line</td>
<td>89 (29.7%)</td>
<td>23 (29.1%)</td>
<td>66 (29.9%)</td>
</tr>
<tr>
<td>≥ IV line</td>
<td>44 (14.7%)</td>
<td>8 (10.1%)</td>
<td>36 (16.3%)</td>
</tr>
<tr>
<td>Type of treatment‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nivolumab</td>
<td>239 (79.7%)</td>
<td>61 (77.2%)</td>
<td>178 (80.5%)</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>25 (8.3%)</td>
<td>8 (10.1%)</td>
<td>17 (7.7%)</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>22 (7.3%)</td>
<td>6 (7.6%)</td>
<td>16 (7.2%)</td>
</tr>
<tr>
<td>Avelumab</td>
<td>6 (2%)</td>
<td>3 (3.8%)</td>
<td>3 (1.4%)</td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>2 (0.7%)</td>
<td>0 (0%)</td>
<td>2 (0.9%)</td>
</tr>
<tr>
<td>Immunotherapy combinations</td>
<td>4 (1.3%)</td>
<td>1 (1.3%)</td>
<td>3 (1.4%)</td>
</tr>
<tr>
<td>Chemo-immunotherapy</td>
<td>2 (0.7%)</td>
<td>0 (0%)</td>
<td>2 (0.9%)</td>
</tr>
<tr>
<td>Best response†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>7 (2.3%)</td>
<td>0 (0%)</td>
<td>7 (3.1%)</td>
</tr>
<tr>
<td>Partial response</td>
<td>94 (31.3%)</td>
<td>23 (29.1%)</td>
<td>71 (32.1%)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>167 (55.7%)</td>
<td>37 (46.8%)</td>
<td>70 (31.7%)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>82 (27.3%)</td>
<td>19 (24%)</td>
<td>63 (28.5%)</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>10 (3.3%)</td>
<td>0 (0%)</td>
<td>10 (4.5%)</td>
</tr>
<tr>
<td>Cause of death¶</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer related</td>
<td>58 (85.3%)</td>
<td>12 (75%)</td>
<td>46 (88.5%)</td>
</tr>
<tr>
<td>Treatment related</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Flu syndrome related</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Other/unknown</td>
<td>10 (14.7%)</td>
<td>4 (25%)</td>
<td>6 (11.5%)</td>
</tr>
</tbody>
</table>

† Best response was evaluated by RECIST 1.1 criteria, according to the local clinical practice of all the participating centers.
‡ Other primary malignancies were represented by head & neck carcinoma, urothelial cancer, gastric cancer and colon adenocarcinoma.
§ Immune checkpoint inhibitors were used as monotherapy when not otherwise expressly specified.
¶ 232 patients were censored at the data cutoff (30 May 2017); 68 events.

while five developed IS before starting CKI treatment, with median time interval of 3.1 months (IQR = 2–3.5). Almost all vaccinated patients developing IS (18/19) had the occurrence of the illness after the administration of the flu shot, with median time interval of 2.6 months (IQR = 1.5–4.8).

**Influenza syndrome morbidity**

The incidence of IS in the overall study population was of 15% (45/300). It was higher in the lung cancer subgroup, reaching 20% of cases.

The incidence of IS was of 24.1% among patients receiving the vaccine (19/79), compared with that of 11.8% in the unvaccinated control group (26/221); OR: 2.4; 95% CI: 1.23–4.59; p = 0.009 (Figure 1).

**Influenza syndrome lethality & severity**

No cases of flu-related death were reported. Overall, eight patients had at least one influenza recurrence: four (19.1%) vaccinated and four (15.4%) unvaccinated cases (p = 0.62). Three vaccinated patients required intravenous therapy in day-hospital regimen due to flu-related symptoms (15.8%) versus two cases in the control group (7.7%), p = 0.39. Five vaccinated patients required hospitalization due to IS (26.3%) versus four unvaccinated (15.4%), p = 0.36. No cases of documented bacterial superinfections were reported. Mean duration of IS was similar for vaccinated and unvaccinated patients (respectively 8.2 days ± 3.1 and 8.3 days ± 4.1).

**Anticancer treatment outcome**

No statistically significant differences were seen in terms of ORR, DCR or TTF with CKI therapy, respectively, between vaccinated and control patients or between patients developing IS or not in the overall study population,
Table 2. Results of preliminary univariate and multivariate analyses for overall survival in the overall study population.

<table>
<thead>
<tr>
<th>Clinical variable</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male vs female)</td>
<td>OR 1.25 (0.73–2.14) p = 0.42</td>
<td>–</td>
</tr>
<tr>
<td>Age (years)</td>
<td>OR 1.00 (0.97–1.03) p = 0.99</td>
<td>–</td>
</tr>
<tr>
<td>Line (&gt; = 3 vs 1–2)</td>
<td>OR 0.82 (0.51–1.33) p = 0.42</td>
<td>–</td>
</tr>
<tr>
<td>Influenza vaccine (yes vs no)</td>
<td>OR 0.75 (0.43–1.32) p = 0.32</td>
<td>–</td>
</tr>
<tr>
<td>IS (yes vs no)</td>
<td>OR 0.48 (0.21–1.12) p = 0.09</td>
<td>OR 0.35 (0.15–0.84) p = 0.02</td>
</tr>
<tr>
<td>Influenza vaccine and/or IS (yes vs no)</td>
<td>OR 0.68 (0.41–1.16) p = 0.16</td>
<td>–</td>
</tr>
<tr>
<td>ORR (yes vs no)</td>
<td>OR 0.06 (0.02–0.20) p &lt; 0.0001</td>
<td>OR 0.15 (0.04–0.50) p = 0.002</td>
</tr>
<tr>
<td>DCR (yes vs no)</td>
<td>OR 0.08 (0.04–0.13) p &lt; 0.0001</td>
<td>OR 0.11 (0.06–0.21) p &lt; 0.0001</td>
</tr>
</tbody>
</table>

DCR: Disease control rate; IS: Influenza syndrome; OR: Odds ratio (95% confidence intervals in brackets); ORR: Objective response rate.

nor considering the patient population starting CKI treatment closer to the vaccinal season. With the limitation of immature data, statistically significant results of preliminary univariate and multivariate analyses for OS are reported in Table 2.

**Lung cancer subgroup**

In the population of 103 non-small-cell lung cancer patients, mOS was not reached (76 censored); mTTF was of 10.2 months (95% CI: 6.8–13.6; 40 censored).

Flu incidence in vaccinated patients reached 27% of cases (9/33) versus 17% for unvaccinated patients (12/70); OR: 1.81; 95% CI: 0.67–4.86; p = 0.29.

No statistically significant differences were seen in terms of ORR, DCR or TTF according to the vaccinal status and/or to IS occurrence. Despite immature data for OS, a statistically significant positive correlation with flu vaccine administration and/or IS development was demonstrated in this subgroup: 1-year OS 86.7% (95% CI: 75.7–97.7) for vaccine/IS group versus 66.7% (95% CI: 53.6–79.8), p = 0.02 (Figure 2). Significance was maintained at the multivariate analysis (Table 3).
Figure 2. Overall survival in lung cancer patients according to vaccine and/or influenza syndrome status (103 patients).

Table 3. Results of preliminary univariate and multivariate analysis for overall survival in the lung cancer subgroup (103 patients).

<table>
<thead>
<tr>
<th></th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
</table>
| Gender (male vs female) | OR 1.31 (0.49–3.46)  
|                       | p = 0.59                            |                             |
| Age (years)          | OR 1.03 (0.58–1.08)  
|                       | p = 0.20                            |                             |
| Treatment line (≥ 3 vs 1–2) | OR 0.74 (0.30–1.83)  
|                       | p = 0.51                            | OR 0.29 (0.11–0.78)  
|                       |                                     | p = 0.01                    |
| Influenza vaccine (yes vs no) | OR 0.43 (0.16–1.13)  
|                       | p = 0.08                            |                             |
| IS (yes vs no)       | OR 0.31 (0.07–1.30)  
|                       | p = 0.10                            |                             |
| Influenza vaccine and/or IS (yes vs no) | OR 0.39 (0.16–0.92)  
|                       | p = 0.03                            | OR 0.29 (0.11–0.74)  
|                       |                                     | p = 0.008                   |
| ORR (yes vs no)      | OR 0.02 (0.01–0.68)  
|                       | p = 0.03                            | NE                          |
| DCR (yes vs no)      | OR 0.08 (0.04–0.19)  
|                       | p < 0.0001                          | OR 0.06 (0.03–0.15)  
|                       |                                     | p < 0.0001                  |

DCR: Disease control rate; IS: Influenza syndrome; NE: Not evaluated; OR: Odds ratio (95% confidence intervals in brackets); ORR: Objective response rate.

Elderly subgroup

Prespecified subgroup analysis of IS incidence basing on age, with the calculated cutoff of 71 years, demonstrated similar rates of flu infections in the younger subgroup (≤71 years, 198 patients), respectively 14.3% for vaccinated and 14.1% for unvaccinated patients. The incidence of IS was instead significantly different according to the vaccinal status in the subgroup of elderly (>71 years, 102 patients), with rate of IS reaching 37.8% for vaccinated patients, versus 6.1% for unvaccinated cases, OR: 9.28; 95% CI: 2.77–31.14; p < 0.0001 (Figure 3).

The DCR of elderly patients (102 cases) was higher when vaccinated, respectively 83.8 versus 64.6%, OR: 2.83; 95% CI: 1.03–7.78; p = 0.039. IS occurrence did not impact on DCR. No statistically significant differences were seen in terms of ORR according to the vaccinal status in the elderly group, but better ORR was demonstrated for patients developing IS, with 52.6 versus 28.9% for unaffected patients (irrespective of the vaccinal status), OR: 2.73; 95% CI: 0.99–7.56; p = 0.048. mTTF was of 11.3 months for elderly (95% CI: 5.12–17.44), and it remained unaffected by vaccination and/or IS. Preliminary OS analyses in this subgroup were not significant (mOS not reached, 82 censored).
Flu vaccine indication during cancer immunotherapy

Rates of influenza syndrome (%)

<table>
<thead>
<tr>
<th>Group</th>
<th>Rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Younger patients (≤ 71 years)</td>
<td>14.1% 14.3%</td>
</tr>
<tr>
<td>Elderly patients (&gt; 71 years)</td>
<td>6.1% 37.8%</td>
</tr>
</tbody>
</table>

Figure 3. Incidence of influenza syndrome according to the vaccinal status in the younger patients’ subgroup and in the elderly patients’ subgroup, respectively.

Discussion

To our knowledge, the INVIDIa study is the first published study investigating the clinical efficacy of influenza vaccine in cancer patients undergoing immune checkpoint blockade. According to the study results, it seems that flu vaccine was not clinically effective in advanced cancer patients treated with CKI. The incidence of IS occurrence was much higher for the vaccinated group than for the nonvaccinated one (Figure 1). This phenomenon cannot be justified by vaccine-derived flu-like adverse reactions, because of the prolonged time frame from vaccine administration to IS occurrence and the unequivocal definition of IS.

The clinical ineffectiveness of influenza vaccine was even more pronounced among elderly, relating to the highest flu morbidity (Figure 3). This is not justified by a hypothetically greater expected morbidity of influenza in the elderly: flu incidence is contrariwise generally lower in elderly populations [24–26].

During the 2016–2017 flu season in Italy, the cumulative incidence of IS was around 6.8%; incidence rates among elderly (> 65 years) ranged from 0.3 to 6.3%; vaccinal coverage was of 22%; 95% of serious cases and 100% of lethal cases occurred in subjects with pre-existing chronic disease [24,25].

In our study population, the severity of IS was instead quite mild, with no flu-related deaths and low rates of complications, irrespective of the vaccinal status. The increased morbidity of influenza did not negatively impact the clinical outcome of affected patients. We hypothesized that CKI treatment may have been responsible for a greater immunocompetence against viral infections, preserving patients from severity and lethality of IS. This assumption is supported by preclinical evidence, demonstrating that the therapeutic inhibition of PD-1/PD-L1 binding in the airways can prevent the T-cell impairment provoked by influenza virus and enhances CD8⁺ T-cell function and viral clearance, reducing viral titers, mitigating airway dysfunction and accelerating infection recovery in mice [27,28].

Of note, in the INVIDIa population, similar times of duration of symptoms and similar rates of recurrence and hospitalizations were demonstrated among patients with IS irrespective of the flu shot administration, suggesting that the vaccine was not helpful in further mitigating the severity of IS.

A possible scientific rationale for an increased incidence of infection in vaccinated CKI-treated patients, comes from the evidence that an enhanced aberrant T-cell response could paradoxically contribute to the IS immunopathology [29]. After initial influenza virus contagion, T cells become responsible for detrimental effects if immune response is excessive, contributing to damage (probably mediated by TNF-α) and to the flu development [30]. A detrimental role of CD8⁺ T cells was already demonstrated in the 1980s, when nude mice showed a delay in pathology, morbidity and mortality from influenza virus infection compared with those of wild-type animals [31]. Interestingly, the adoptive transfer of specific T cells, or of viral peptide-loaded dendritic cells, on mice models, respectively caused lethal lung injury and elicited a strong T CD8⁺ response in the absence of viral infection [28,32]. This suggests that also only vaccination could trigger the detrimental effect. Immune checkpoint blockade might upset the critical balance between the number and function of T cells, which is required for virus clearance and that which is responsible for harmful effects, increasing the flu morbidity even more in vaccinated patients, who received an additional antigenic stimulus.
Considering the study results, the counseling of CKI-treated cancer patients about influenza vaccine should not exempt from notifying them of its possible clinical ineffectiveness and of its potential uselessness.

A separated reflection should be deserved for lung cancer patients, showing high influenza morbidity and less pronounced clinical ineffectivity of flu vaccine. For them, vaccination and/or IS development inexplicably resulted in a better survival, irrespective of the anticancer treatment outcome. Precautionary vaccinal measures, although possibly not useful, but obviously not harmful, may be undertaken with prudent intent at least in this subgroup.

The second key issue of the study seems to find a reassuring reply. Flu vaccine did not negatively affect treatment outcome, in terms of ORR, DCR or TTF. Conversely, in some cases it even correlated with better treatment efficacy.

Translating such evidence in terms of counseling, patients could be reassured about the likely innocuousness of the vaccine against the effectiveness of anticancer therapy.

Interestingly, also IS occurrence, in some cases, was related to a better treatment outcome. Vaccine-induced or influenza-induced antigen stimulation may similarly positively impact the cell-mediated immune response to CKI treatment, acting as analogous immunogenic stimuli. This concept is anything but new: at the end of the 19th century, William Coley provoked antitumor immune responses by injecting cancer patients with bacteria or bacterial products [33]. Moreover, a relationship between feverish infection and concurrent spontaneous remission from cancer has been known for a very long time [34]. In the INVIDIa population, the immune activation given by the viral particles of the split vaccine, and furthermore by the infection itself, may have been synergistic to CKI, contributing to the final antitumor effect.

The main limitation of the study is represented by its retrospective nature. The inclusion criteria, considering patients receiving therapy in a prespecified time lapse, irrespective of treatment starting, potentially represent a positive selection bias: nevertheless, the study end points have been compared within the study population, preserving the internal validity, also considering the relatively good balance of the two groups (Table 1). A further selection bias could have been determined by vaccination, since it is possible that patients with higher clinical risk (e.g., with more underlying chronic diseases) were more likely to be vaccinated, possibly influencing IS incidence in the vaccinated subgroup. However, such issue does not compromise the validity of the study, because, precisely in those more fragile patients, it is useful to observe the effectiveness of the vaccine. The limitations of not including irAEs and vaccine-related adverse events among the study end points, and to not collecting the vaccine type, were due to the expected scarce reliability of such retrospective data. Furthermore, the retrospective nature did not permit to verify serum viral titers to confirm the clinically assessed IS. Finally, although the analysis of high-risk subgroups (such as lung cancer patients and the elderly) was necessary in relation to the relevance of their indication to flu vaccine, the relatively limited sample size for subgroup analyses suggests caution in their interpretation. Survival data are still immature.

**Conclusion**

The INVIDIa study suggests that although influenza vaccine may be clinically ineffective and unnecessary in advanced cancer patients receiving CKI treatment, it seems not to compromise their clinical outcome and not to negatively impact the efficacy of anticancer therapy.

**Future perspective**

Since, due to the limitation of the retrospective nature, the evidence provided by the INVIDIa study is not sufficiently robust to change clinical practice, we are planning the INVIDIa-2 study, a prospective, multicenter, observational trial to definitely address the issue.

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**Ethical disclosure**

The INVIDIa study obtained institutional review board approval by the Local Ethical Committee of the participating institutions. All participating patients signed an informed consent for the anticancer immunotherapy.
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Supplementary data
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Executive summary

• International guidelines strongly recommend influenza vaccination in patients with cancer as safe and minimally invasive.
• Very few data supported the use of flu vaccine during immunotherapy with immune checkpoint inhibitors up to date.
• The INVIDIa study, on a population of 300 advanced cancer patients treated with immune checkpoint inhibitors, evidenced a higher incidence of influenza syndrome in vaccinated (24.1%) versus unvaccinated patients (11.8%; \( p = 0.009 \)).
• No flu-related deaths and mild severity of influenza syndrome were reported in the study population irrespective of vaccination.
• No negative impact of flu vaccination on the anticancer treatment efficacy was found in the overall population: treatment outcomes were even significantly better with vaccine and/or flu development in some subgroups.
• Clinical ineffectiveness of flu vaccine was more marked in the elderly.
• Although influenza vaccine could be ineffective and unnecessary in advanced cancer patients undergoing treatment with immune checkpoint inhibitors, it seems to not compromise their clinical outcome and to not negatively impact the efficacy of anticancer therapy.

References


