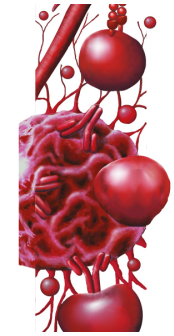
Short Communication

Immunotherapy



Impact of influenza syndrome and flu vaccine on survival of cancer patients during immunotherapy in the INVIDIa study

Melissa Bersanelli*[1,2], Sebastiano Buti[1], Giuseppe Luigi Banna[3], Ugo De Giorgi[4], Alessio Cortellini[5,6], Sara Elena Rebuzzi[1,7], Marcello Tiseo[1,2], Giuseppe Fornarini[7], Francesca Mazzoni[8], Stefano Panni[9], Michele De Tursi[10], Pietro Di Marino[10], Sabrina Rossetti[11], Ernesto Rossi[12], Silverio Tomao[13], Emmanuele De Luca[14], Mariella Sorarù[15], Claudia Mucciarini[16], Francesco Atzori[17], Leonardo La Torre[18], Maria Giuseppa Vitale[19], Valentino Martelli[7], Pierangela Sepe[20], Veronica Mollica[21], Vanja Vaccaro[22], Giovanni Schinzari[12], Corrado Ficorella[6,7], Francesco Massari[21], Antonio Maestri[18], Roberto Sabbatini[19], Teodoro Sava[15], Massimo Di Maio[14], Elena Verzoni[20], Giuseppe Procopio[20] & Diana Giannarelli[23]

[1]Medical Oncology Unit, University Hospital of Parma, Parma, Italy
[2]Department of Medicine & Surgery, University of Parma, Parma, Italy
[3]Medical Oncology, Cannizzaro Hospital, Catania, Italy
[4]Medical Oncology, Scientific Institute of Romagna for The Study & Treatment of Tumors (IRST) IRCCS, Meldola, Italy
[5]Medical Oncology Unit, St Salvatore Hospital, L'Aquila, Italy
[6]Department of Biotechnological & Applied Clinical Sciences, St Salvatore Hospital, University of L'Aquila, L'Aquila, Italy
[7]Medical Oncology Unit 1, IRCCS Policlinico San Martino Hospital, Genova, Italy
[8]Medical Oncology Unit, Careggi University Hospital, Firenze, Italy
[9]Medical Oncology Unit, ASST – Istituti Ospitalieri Cremona Hospital, Cremona, Italy
[10]Department of Medical, Oral & Biotechnological Sciences & CeSI-MeT, University G. D'Annunzio, Chieti-Pescara, Italy
[11]Dipartimento Corp-S Assistenziale dei Percorsi Oncologici Uro-Genitale, S.S.D Oncologia Clinica Sperimentale Uro-Andrologica, Istituto Nazionale Tumori "Fondazione G. Pascale", IRCCS, Napoli, Italy
[12]Medical Oncology, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy
[13]Department of Medical & Surgical Sciences & Biotechnology, University "La Sapienza", Latina, Italy
[14]Medical Oncology, Ordine Mauriziano Hospital, University of Turin, Torino, Italy
[15]Medical Oncology, Camposampiero Hospital, Padova, Italy
[16]Medical Oncology Unit, Ramazzini Hospital, Carpi, Italy
[17]Medical Oncology, Department of Medical Sciences "M. Aresu", University Hospital & University of Cagliari, Cagliari, Italy
[18]Medical Oncology Department, Santa Maria della Scaletta Hospital, Imola, Italy
[19]Medical Oncology Unit, University Hospital of Modena, Modena, Italy
[20]Genito-Urinary Oncology Unit, Fondazione IRCCS Istituto Nazionale Tumori of Milan, Milano, Italy
[21]Division of Oncology, Sant'Orsola-Malpighi Hospital, Bologna, Italy
[22]Oncology Unit 1, Regina Elena National Cancer Institute, IRCCS, Rome, Italy
[23]Biostatistical Unit, Regina Elena National Cancer Institute, IRCCS, Rome, Italy
*Author for correspondence: Tel.: +39 0521 702 316; bersamel@libero.it

Aim: INVIDIa was a retrospective, multicenter study, exploring the clinical efficacy of influenza vaccine in 300 cancer patients undergoing immunotherapy. Overall survival (OS) was immature at the initial report. **Methods:** We reported the final OS analysis from the original study population and within subgroups. **Results:** Both at the univariate and multivariate analysis, the occurrence of influenza syndrome (IS) was significantly related to better OS in the overall population (OR: 0.53 [95% CI: 0.32–0.88]; p = 0.01). In the lung cancer subgroup, receiving flu vaccine and/or developing IS was related to better OS (p = 0.04). Within elderly patients, the flu vaccine was the main variable for the relative OS advantage (p = 0.05). **Conclusion:** Receiving the flu vaccine and/or developing IS was related to better OS within the INVIDIa population.

First draft submitted: 8 October 2019; Accepted for publication: 10 February 2020; Published online: 24 February 2020

Keywords: flu vaccine • immune checkpoint inhibitors • immunotherapy • influenza syndrome • influenza vaccination • overall survival

Future Medicine

Background

The issue of vaccinating cancer patients against the influenza virus can be easily approached when considering the oncological population receiving chemotherapy or radiotherapy [1]. Given the impaired immunity and the increased risk of influenza-related complications of this subgroup [2], international and national guidelines recommend influenza vaccination in such cancer patients [3–5]. On the other hand, the choice of vaccinating advanced cancer patients undergoing immunotherapy with anti-PD-1/PD-L1 or anti-CTLA-4 immune checkpoint inhibitors (CKI) is currently supported by scarce and conflicting evidence [6].

The INVIDIa study was originally planned to assess the clinical efficacy of the influenza vaccine in advanced cancer patients undergoing immunotherapy with CKI [7]. The primary end point of the study was the incidence of influenza syndrome (IS) in the overall population, clinically 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) [7]. Prespecified subgroup analyses were planned for lung cancer patients and for the elderly. Moreover, the potential impact of the vaccine in terms of severity and mortality of IS and on the outcome of anticancer immunotherapy has been explored. The study enrolled 300 advanced cancer outpatients: 79 received influenza vaccination (26.3%) in the form of the trivalent (two type A viruses, H1N1 and H3N2, and one type B virus, B/Brisbane) or quadrivalent (adding a type B virus, B/Phuket) inactivated virus vaccine, while the remaining 221 patients did not. In the overall study population, 15% of patients developed IS (in the lung cancer subgroup, 20% of patients developed IS). The incidence of IS was unexpectedly higher (24.1%) among patients receiving the vaccine, compared with that in the unvaccinated control group (11.8%), with an odds ratio of 2.4 (95% CI: 1.23–4.59); p = 0.009. Nevertheless, IS demonstrated mild severity (irrespective of the vaccine) and no flu-related deaths were recorded within the whole population. Another crucial point explored in the study was the impact of flu vaccination on the oncological outcome, especially considering the potential interference between two different kinds of immunological stimuli. This issue seems to be ruled out: the flu vaccine did not negatively affect treatment response or duration in the study population. Conversely, in the elderly subgroup of patients (>71 years), it even correlated with better treatment efficacy for vaccinated individuals compared with unvaccinated subjects in terms of disease control rate (defined as the cumulative rate of stable diseases, partial and complete responses), while a better objective response rate (defined as the rate of complete and partial responses) was even demonstrated for elderly patients developing IS (irrespective of the vaccinal status) compared with that of elderly subjects without IS [8]. Considering such unexpected findings, the overall survival (OS) analysis was considered of high interest for a more reliable interpretation. At the time of the initial report [8], the median OS (mOS) was still not reached at the median follow-up of 12.2 months (232 censored) and immunotherapy was still ongoing for 149 patients. Nevertheless, preliminary findings from multivariate analysis at the time of the first study publication showed a positive correlation between IS occurrence and OS in the overall study population. Moreover, receiving the influenza vaccine and/or developing IS seemed related to better OS in the lung cancer patient subgroup, according to both univariate and multivariate analyses. In the elderly subgroup, no difference in terms of OS was found at the preliminary analysis basing on vaccine and/or IS. Since the first report of the INVIDIa study was largely immature for OS, we reported herein the updated final results, with data cut-off in March 2019.

Patients & methods

INVIDIa was a retrospective, observational, multicenter study, conducted at the medical oncology units of 21 Italian centers, after approval by the respective local ethical committees [8]. Records of consecutive advanced cancer outpatients receiving treatment with CKI during the Italian influenza season 2016–2017 (from 1 November 2016 to 30 May 2017) were collected. Inclusion criteria were any primary advanced cancer and any systemic treatment with anti-programmed cell death receptor 1 (PD-1), anti-PD-1 ligand (PD-L1) or anti-cytotoxic T-lymphocyte antigen 4 (CTLA-4) antibodies. Detailed information regarding influenza vaccination, IS occurrence and treatment with CKI was retrospectively investigated. IS, according to the definition adopted by the Italian Ministry of Health at the time of the study planning, 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) [7]. The primary end point of the study was the incidence of IS in the overall population. Aside from several secondary end points inherent to severity and lethality of IS, the impact

Table 1. Results of univariate and multivariate analyses for overall survival in the overall study population.

	Univariate analysis	Multivariate analysis
Gender (males vs females)	1.09 (0.77–1.54) p = 0.63	–
Age (>71 years vs ≤71)	0.99 (0.98–1.01) p = 0.37	–
Line (≥3 vs 1-2)	0.97 (0.70–1.33) p = 0.83	–
Vaccine (yes vs no)	0.80 (0.55–1.16) p = 0.24	–
IS (yes vs no)	0.60 (0.36–0.99) p = 0.049	0.53 (0.32–0.88) p = 0.01
Vaccine a/o flu (yes vs no)	0.71 (0.50–0.99) p = 0.044	–
ORR (yes vs no)	0.16 (0.11–0.22) p < 0.0001	0.43 (0.27–0.69) p < 0.0001
DCR (yes vs no)	0.08 (0.04–0.13) p < 0.0001	0.22 (0.15–0.32) p < 0.0001

IS: Influenza syndrome; DCR: Disease control rate; ORR: Objective response rate.

of influenza vaccine and of IS on the outcome of patients was investigated, including analyses for OS, defined from therapy starting to death for any reason. All the prespecified end points were explored within subgroups of interest, namely, lung cancer patients and elderly patients (> 71 years).

The original analyses for OS, defined from immunotherapy starting to death for any reason, were repeated herein, after update of the original databases by all the involved centers, with data cut-off in March 2019. Median follow-up was calculated with the Kaplan-Meier reverse method. The survival curves were estimated with the Kaplan–Meier method and the outcomes were compared between groups using the log-rank test. Cox proportional hazard model was used to estimate hazard ratio (HR) and 95% CI: for each factor and in a multivariate analysis, including all the evaluable parameters, using a forward stepwise selection method. $p < 0.05$ was considered as a threshold for statistical significance. Subgroup analyses were performed for lung cancer patients and for elderly patients, using as prespecified cut-off the median age of the vaccinated subgroup at the time of flu vaccine administration. Age for the unvaccinated group was calculated at the start of the observation period.

Results

The characteristics of the INVIDIa study population are reported in Supplementary Table 1. In the overall population, mOS was 27.6 months (95% CI: 22.1–33.1) at the median follow-up of 31 months (147 censored). Immunotherapy was still ongoing for 63 patients at the data cutoff.

Final results of univariate and multivariate analyses for OS in the overall population are reported in Figure 1 and Table 1. Flu vaccine alone did not impact on OS (HR: 0.80 [95% CI: 0.55–1.16]; p = 0.24, Figure 1A). Contrarywise, the occurrence of IS was significantly related to better OS, with mOS of 36.9 months of patients developing IS versus 26.1 months for unaffected patients (HR: 0.60 [95% CI: 0.36–0.99]; p = 0.047, Figure 1B). 2-year OS was 69.7% (95% CI: 56.0–83.4) for patients developing IS versus 51.6% (95% CI: 45.3–57.9) of unaffected patients. Significance was maintained at the multivariate analysis (HR: 0.53 [95% CI: 0.32–0.88]; p = 0.01, Table 1): IS and objective response rate were the only variables with confirmed correlation to OS. Considering both variables, patients who received the vaccine and/or developed IS seemed to live significantly longer than patients without IS nor vaccination, with mOS of 31.5 months versus 23.1 months, (HR: 0.71 [95% CI: 0.50–0.99]; p = 0.044, Figure 1C). In the overall population, 2-year OS was 62.8% (95% CI: 53.2–72.4) for vaccine/IS group versus 49.8% (95% CI: 42.5–57.1) of controls.

Non-small cell lung cancer patients

In the subgroup of 103 non-small-cell lung cancer patients, mOS was 20.9 months (95% CI: 13.1–28.7, 44 censored). Confirming the preliminary findings, also in this subgroup a statistically significant positive correlation of OS with flu vaccine administration and/or IS development was demonstrated, with mOS of 27.7 months versus 15.5 months (HR: 0.58 [95% CI: 0.34–0.99]; p = 0.04, Figure 2); 2-year OS was 60.1% (95% CI: 44.8–75.4) for patients with vaccine/IS versus 38.1% (95% CI: 25.4–50.8) of controls. Significance was maintained at the

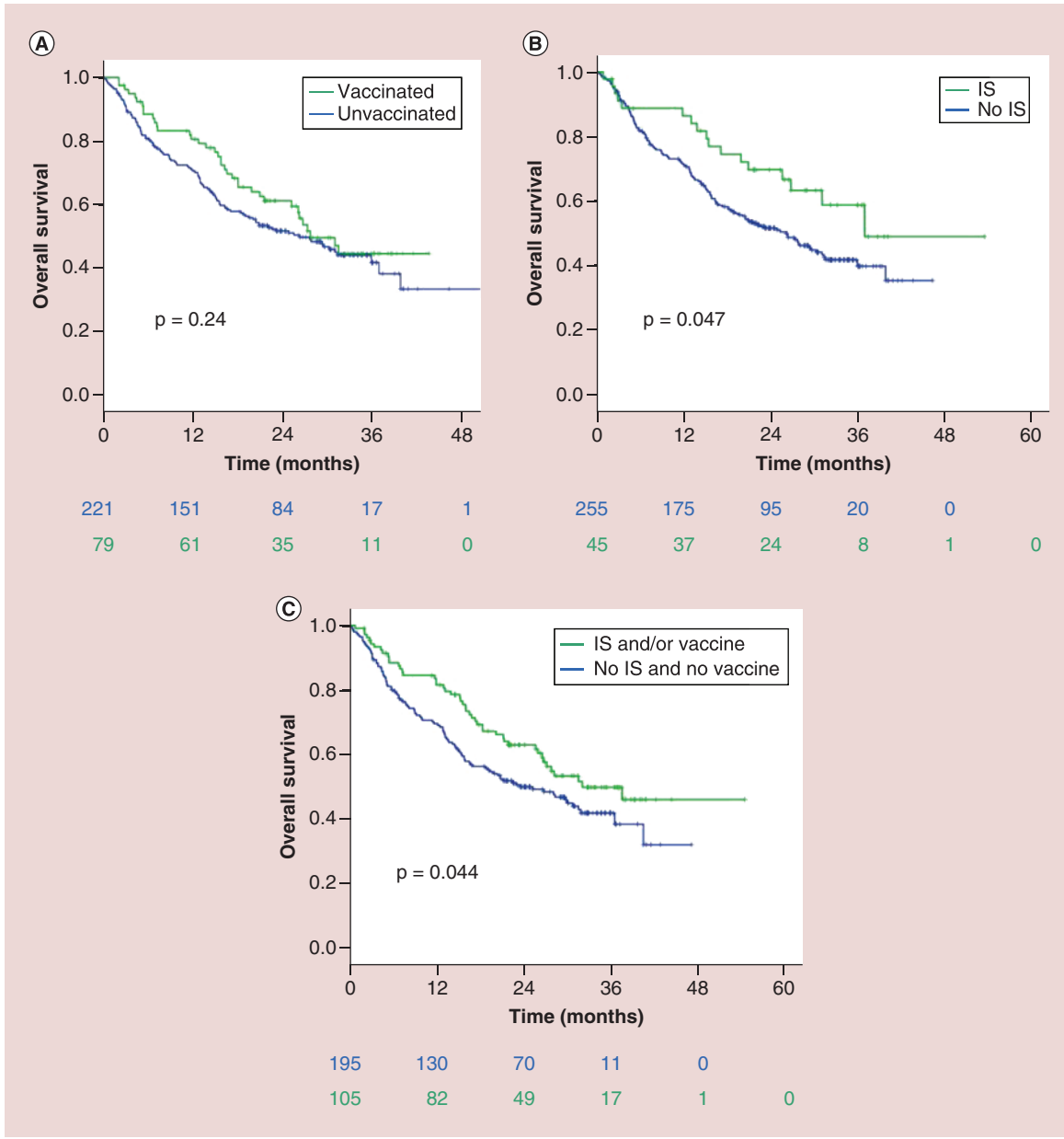


Figure 1. Final results for overall survival in the INVIDIa study population. (A) Flu vaccine alone did not impact on overall survival (OS). **(B)** The occurrence of IS was significantly related to better OS (median OS 36.9 months of patients developing IS vs 26.1 months for unaffected patients). **(C)** Patients who received the vaccine and/or developed IS seemed to live significantly longer than patients without IS nor vaccination (mOS of 31.5 vs 23.1 months).
IS: Influenza syndrome.

multivariate analysis (HR: 0.48 [95% CI: 0.27–0.85]; p = 0.01, Table 2). In this case, the single variables did not reach statistical significance in terms of impact on OS (p = 0.19 and p = 0.30 respectively; Supplementary Figures 1 & 2).

Elderly patients

In the elderly subgroup (102 patients over 71 years, mOS 26.1 months, 52 censored), there was a correlation between flu vaccine administration and better OS, with mOS not yet reached among vaccinated elderly patients versus 18.7 months for unvaccinated (HR: 0.49 [95% CI: 0.26–0.93]; p = 0.03, Figure 3A) and with 2-year OS of 67.7% (95% CI: 52.0–83.4) of vaccinated versus 43.1% (95% CI: 30.4–55.8) of unvaccinated elderly. On the

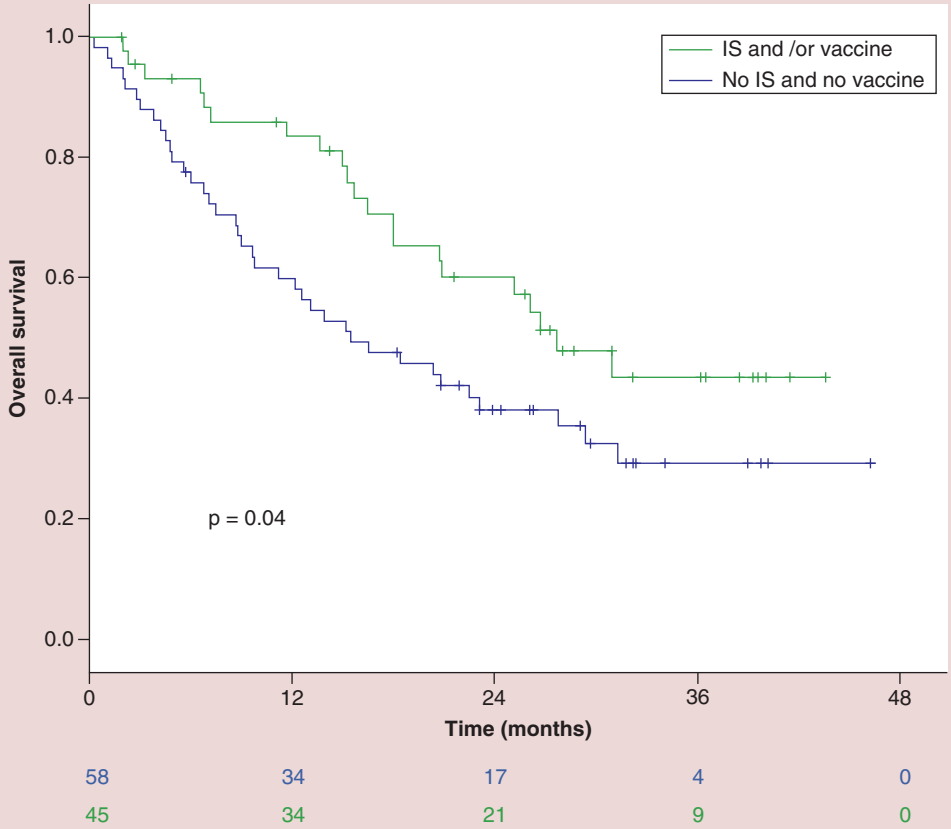


Figure 2. Final overall survival results in the subgroup of 103 non-small-cell lung cancer patients. A statistically significant positive correlation of overall survival (OS) with flu vaccine administration and/or IS development was demonstrated (median OS of 27.7 vs 15.5 months).
IS: Influenza syndrome.

Table 2. Results of univariate and multivariate analysis for overall survival in the lung cancer subgroup (103 patients).

	Univariate analysis	Multivariate analysis
Gender (males vs females)	1.20 (0.63–2.26) p = 0.58	–
Age (>71 years vs ≤71)	1.04 (1.01–1.07) p = 0.01	1.05 (1.02–1.08) p = 0.004
Treatment Line (≥ 3 vs 1–2)	1.03 (0.59–1.79) p = 0.92	0.43 (0.22–0.82) p = 0.01
Flu vaccine (yes vs no)	0.74 (0.42–1.31) p = 0.30	–
IS (yes vs no)	0.62 (0.31–1.27) p = 0.19	–
Vaccine and/or IS (yes vs no)	0.58 (0.34–0.99) p = 0.04	0.48 (0.27–0.85) p = 0.01
ORR (yes vs no)	0.30 (0.15–0.60) p = 0.001	–
DCR (yes vs no)	0.19 (0.11–0.34) p < 0.0001	0.15 (0.08–0.27) p < 0.0001

DCR: Disease control rate; IS: Influenza **syndrome; ORR: Objective response rate.**

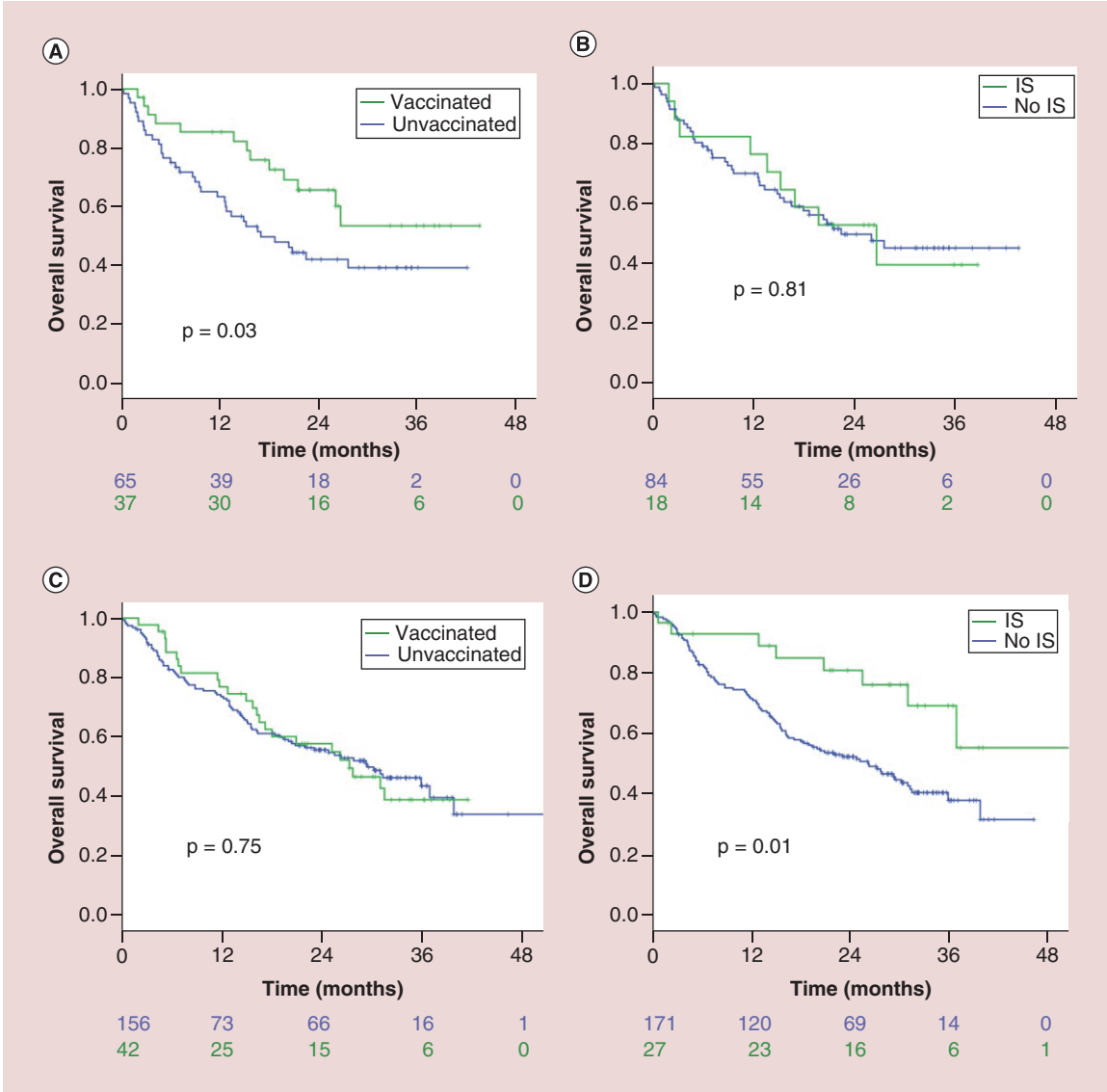


Figure 3. Final overall survival results in the elderly subgroup (A and B, 102 patients over 71 years) and in the complementary nonelderly subgroup (C and D, 198 patients). (A) Median overall survival (mOS) was not yet reached among vaccinated elderly patients versus 18.7 months for unvaccinated. **(B)** The development of IS did not impact survival of elderly patients. **(C)** OS curves according to flu vaccine administration were almost overlapped for nonelderly patients, with any significant difference (mOS of 26.7 and 26.1 months, respectively, for vaccinated and unvaccinated). **(D)** IS occurrence was related to significantly better survival for nonelderly patients, with mOS not yet reached for patients developing IS against 26.2 months for unaffected patients.
IS: Influenza syndrome.

other hand, the development of IS did not impact survival of elderly patients (p = 0.81, Figure 3B). None of such variables were confirmed as significant at the multivariate analysis (Supplementary Table 2).

In the complementary nonelderly subgroup (198 patients), IS occurrence was related to significantly longer survival, with mOS not yet reached for patients developing IS against 26.2 months for unaffected patients (p = 0.01, Figure 3D). On the contrary, OS curves according to flu vaccine administration were almost overlapped, with any significant difference (mOS of 26.7 and 26.1 months, respectively, for vaccinated and unvaccinated; p = 0.96; Figure 3C).

Considering the alternative cutoff of 65 years, corresponding to that adopted by guidelines for flu vaccine recommendation, the favorable impact of the vaccine on OS of elderly was lost, despite wider sample size (187 patients ≥65 years; p = 0.17, Supplementary Figure 3).

Discussion

The final results from the INVIDIa study confirm the same direction of the preliminary findings, showing that receiving flu vaccine and/or developing IS is related to better survival in this population. This partially unexpected evidence possibly suggests the hypothesis that the antigenic stimuli by viral particles, or even more by the wild viral antigen, could improve the outcome of advanced cancer patients treated with CKI immunotherapy.

Considering both variables, either the vaccine and/or IS, their presence was related to longer OS in the overall population. Nevertheless, the greater weight of such favorable impact could have been played by IS more than by the vaccine. This effect was less marked in the non-small-cell lung cancer patient subgroup, probably due to the small sample size and to the possibly higher morbidity of IS among lung cancer patients. Similarly, the favorable impact of IS was less significant among the elderly, maybe due to its higher severity in these frail subjects, or possibly to the immune senescence, that could nullify the immunogenic stimulus of IS. Indeed, when excluding the elderly from the analyses, the favorable impact of IS was clearly enhanced (see Figure 3C), while the lack of any difference between vaccinated and unvaccinated patients was evident (see Figure 3D).

In the INVIDIa study population, the vaccine did not prevent the occurrence of IS, but was even related to its increased incidence [8]. This could constitute a bias for the interpretation of the secondary findings, or otherwise it could provide an immunological explanation for such results. Almost all vaccinated patients in the study developed IS after the administration of the flu shot, with a long median time interval of 2.6 months, thus excluding IS mimicking by reactions to the nonspecific adjuvant of the vaccine. We originally postulated that the major incidence of IS among CKI-treated patients receiving the vaccine could have been due to the occurrence of a paradoxical hypersensitivity reaction to the wild viral antigen after the previous encounter with the vaccinal antigen [9,10]. This event could have enriched the group of patients developing IS with particularly immunoreactive subjects, more capable to respond to CKI and, as a consequence, to achieve better OS. Maybe neither the vaccine nor IS are responsible for improved survival, but IS occurrence as a paradoxical hypersensitivity reaction could represent the signal of a more marked immune capability. Such patients could have been positively selected (by IS occurrence) as the more likely to experience a survival benefit from immunotherapy. Nevertheless, looking at the original results of the study in terms of flu incidence, the paradoxical effect of enhanced IS incidence was much more marked for the elderly than for young patients, laying against this hypothesis [8].

On the other hand, the positive immunogenic effect of influenza antigens could have emerged thanks to the low lethality and severity of IS in the present population, maybe due to an increased immunocompetence of CKI-treated patients compared with those of other oncological populations [11,12]. Within other series, an enrichment of frail patients developing influenza (with consequent complications) could have negatively affected the outcome despite the antigenic stimulus [2].

A final hint that could be derived from our findings is the fact that the usual cutoff of 65 years, currently adopted for flu vaccine recommendation [5], is probably not suitable for this cancer patient population, since it does not discriminate the benefit from receiving vaccine. The alternative cut-off used herein, chosen as the median age of the overall study population [8], probably represents a more suitable threshold to evaluate the benefit from vaccination and/or the risk of IS-related complications.

The main limitation of the study is its retrospective nature. Another criticism is the low reliability of the threshold chosen for statistical significance, set as $p < 0.05$, in the case of multiple analyses. It was considered quite acceptable considering the retrospective and exploratory nature of the study. Eventually, the inclusion criterion within a prespecified time lapse, irrespective of treatment starting, potentially represents a positive selection bias. Nevertheless, the study maintains its internal validity, since the end points have been compared within the study population.

Conclusion

After suggesting that influenza vaccination could be clinically ineffective for IS prevention and would not likely affect the response to anticancer immunotherapy, we showed herein that receiving flu vaccine and/or developing IS was related to better survival within the INVIDIa study population, composed by 300 advanced cancer patients undergoing immunotherapy with CKI [8].

Due to the limitation of the INVIDIa study, these findings should be considered as only explorative and potentially hypothesis generating. To better define and support guidelines for clinical practice, we have planned the INVIDIa-2 study, a prospective, multicenter, observational trial, which is ongoing at 80 Italian oncological centers during the flu season 2019/2020.

Summary points

- **There is conflicting evidence about safely and effectively vaccinating against influenza in advanced cancer patients undergoing immunotherapy with immune checkpoint inhibitors.**
- **We present herein the final overall survival (OS) data of the INVIDIa study, originally planned to assess the clinical efficacy of influenza vaccine in this oncological population.**
- **The occurrence of influenza syndrome (IS) was significantly related to longer OS within the INVIDIa study population, irrespective of the vaccine.**
- **Receiving the flu vaccine and/or developing IS was related to better OS in the overall population and within subgroups.**
- **In the lung cancer subgroup and for elderly patients, OS advantage seemed more attributable to the vaccine than to IS.**

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/imt-2019-0180

Acknowledgments

We gratefully acknowledge all the other colleagues from 21 Italian centers who originally contributed to the data collection for the INVIDIa study: M Santoni, P Castrignanò, E Gambale, R Iacovelli, A Papa, C Lolli, R Ratta, M Michiara, F Leonardi, M Milella, G Facchini, S Bui, C Natoli, E Rapacchi, A Pireddu, H Lipari and F Comito. We gratefully acknowledge the Federation of Italian Cooperative Oncology Groups for promoting the prospective development of the INVIDIa study (INVIDIa-2 and INVIDIa-BIOS studies).

Financial & competing interests disclosure

M Bersanelli received research funding by Roche, Pfizer, Seqirus, AstraZeneca, Bristol-Myers Squibb, Novartis and Sanofi; she also received honoraria for advisory role and as speaker at scientific events by Bristol-Myers Squibb, Novartis and Pfizer. S Buti received honoraria for advisory role and as speaker at scientific events from Pfizer, BMS, IPSEN, Pierre - Fabre, Merck Sharp & Dohme (MSD), AstraZeneca; he also received research funding by Novartis. A Cortellini received honoraria for advisory role and as speaker at scientific events by Bristol-Myers Squibb, Astra Zeneca and MSD. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

References

1. 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.* 2, CD008983 (2018).
2. Cooksley CD, Avritscher EB, Bekele BN, Rolston KV, Geraci JM, Elting LS. Epidemiology and outcomes of serious influenza-related infections in the cancer population. *Cancer* 104(3), 618–628 (2005).
3. Rubin LG, Levin MJ, Ljungman P *et al.* Infectious Diseases Society of America. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. *Clin. Infect. Dis.* 58(3), e44–e100 (2014).
4. Pedrazzoli P, Baldanti F, Donatelli I *et al.* Vaccination for seasonal influenza in patients with cancer: recommendations of the Italian Society of Medical Oncology (AIOM). *Ann. Oncol.* 25(6), 1243–1247 (2014).
5. Grohskopf LA, Sokolow LZ, Broder KR *et al.* Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices–United States, 2018–19 Influenza Season. *Centers for Disease Control and Prevention (CDC) Recommendations and Reports* 67(3), 1–20 (2018).
6. Bersanelli M, Buti S, De Giorgi U *et al.* State of the art about influenza vaccination for advanced cancer patients receiving immune checkpoint inhibitors: when common sense is not enough. *Crit. Rev. Oncol. Hematol.* 139, 87–90 (2019).

7. Italian Ministry of Health: Influnet. Rete Italiana Sorveglianza Influenza. Sistema di Sorveglianza Sentinella dell'influenza basata su Medici di Medicina Generale e Pediatri di Libera Scelta. Sorveglianza Epidemiologica e Virologica. Protocollo Operativo. Stagione influenzale 2012–2013. www.salute.gov.it/imgs/C_17_pubblicazioni_1853_allegato.pdf
8. Bersanelli M, Giannarelli D, Castrignanò P *et al.* INfluenza Vaccine Indication During therapy with Immune checkpoint inhibitors: a transversal challenge. The INVIDIa study. *Immunotherapy* 10(14), 1229–1239 (2018).
9. Hillaire ML, Rimmelzwaan GF, Kreijtz JH. Clearance of influenza virus infections by T cells: risk of collateral damage? *Curr. Opin. Virol.* 3(4), 430–437 (2013).
10. Srikiatkhachorn A, Chintapalli J, Liu J *et al.* Interference with intraepithelial TNF-α signaling inhibits CD8(+) T-cell-mediated lung injury in influenza infection. *Viral Immunol.* 23(6), 639–645 (2010).
11. Weber JS, Hamid O, Chasalow SD *et al.* Ipilimumab increases activated T cells and enhances humoral immunity in patients with advanced melanoma. *J. Immunother.* 35(1), 89–97 (2012).
12. Läubli H, Balmelli C, Kaufmann L *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.* 6(1), 40 (2018).