Impact of influenza vaccination on survival of patients with advanced cancer receiving immune checkpoint inhibitors (INVIDIa-2): final results of the multicentre, prospective, observational study

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Summary

Background The prospective multicentre observational INVIDIa-2 study investigated the clinical effectiveness of influenza vaccination in patients with advanced cancer receiving immune checkpoint inhibitors (ICI). In this secondary analysis of the original trial, we aimed to assess the outcomes of patients to immunotherapy based on vaccine administration.

Methods The original study enrolled patients with advanced solid tumours receiving ICI at 82 Italian Oncology Units from Oct 1, 2019, to Jan 31, 2020. The trial's primary endpoint was the time-adjusted incidence of influenza-like illness (ILI) until April 30, 2020, the results of which were reported previously. Secondary endpoints (data cut-off Jan 31, 2022) included the outcomes of patients to immunotherapy based on vaccine administration, for which the final results are reported herein. A propensity score matching by age, sex, performance status, primary tumour site, comorbidities, and smoking habits was planned for the present analysis. Only patients with available data for these variables were included. The outcomes of interest were overall survival (OS), progression-free survival (PFS), objective response rate (ORR), and disease-control rate (DCR).

Findings The original study population consisted of 1188 evaluable patients. After a propensity score matching, 1004 patients were considered (502 vaccinated and 502 unvaccinated), and 986 of them were evaluable for overall survival (OS). At the median follow-up of 20 months, the influenza vaccination demonstrated a favourable impact on the outcome receiving ICI in terms of median OS [27.0 months (CI 19.5–34.6) in vaccinated vs. 20.9 months (16.6–25.2) in unvaccinated, p = 0.003], median progression-free survival [12.5 months (CI 10.4–14.6) vs. 9.6 months (CI 7.9–11.4), p = 0.049], and disease-control rate (74.7% vs. 66.5%, p = 0.005). The multivariable analyses confirmed the favourable impact of influenza vaccination in terms of OS (HR 0.75, 95% C.I. 0.62–0.92; p = 0.005) and DCR (OR 1.47, 95% C.I. 1.11–1.96; p = 0.007).

Interpretation The INVIDIa-2 study results suggest a favourable immunological impact of influenza vaccination on the outcome of cancer patients receiving ICI immunotherapy, further encouraging the vaccine recommendation in

this population and supporting translational investigations about the possible synergy between antiviral and antitumour immunity.

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Keywords: Influenza-like illness; Influenza vaccination; Flu vaccine; Immune checkpoint inhibitors; Cancer patients; ICI; INVIDIa

Research in context

Evidence before this study

Before the planning of the INVIDIa-2 study, we searched Pubmed, EMBASE, and the Cochrane Library from the database inception until December 5, 2018. The following keywords were used: ("influenza vaccination" or "flu vaccination" or "influenza vaccine") and ("immune checkpoint inhibitors" or "immunotherapy") and ("cancer patients" or "patients with cancer"). The available evidence about influenza vaccination in patients with cancer undergoing immune-checkpoint blockade was limited to a few retrospective studies and limited prospective case series, any of them correlating the oncological outcome to immunotherapy with the vaccinal status. No meta-analyses were available.

Beyond the relevance of the clinical effectiveness of the vaccination in this population, confirmed by the primary results of the study in terms of the reduction of severity and lethality of the influenza-like syndrome in vaccinated patients, it was crucial to verify the potential impact of the vaccine on the efficacy of immune checkpoint inhibitors (ICI), mainly to exclude a harmful immunological interference.

Added value of this study

The INVIDIa-2 trial is the first study demonstrating a higher response rate and more prolonged survival for patients receiving an antiviral vaccination during anticancer treatment with ICI. The final results provided new evidence in favour of administering influenza vaccination to patients with advanced cancer undergoing immunotherapy, showing a favourable impact on the oncological outcome.

Implications of all the available evidence

The present findings, especially in light of prior evidence of a positive impact of bacterial antigens on the anti-tumour response, suggest a synergy between the two different immunological stimuli, namely the immune-checkpoint blockade and the vaccinal split antigen. This concept could guide and help to identify safe and effective immune adjuvants associated with ICI to boost antitumour immunity.

Introduction

In recent years, the awareness about the need for vaccinal protection in patients with cancer has increased over time, partly due to the COVID-19 pandemic and thanks to the availability of new inactivated vaccines against common infections, including influenza, varicella-zoster, pneumococcal pneumonia.[1–4] The consequences of these preventable diseases can be severe or even lethal in immunocompromised and frail subjects, such as patients undergoing anticancer therapy, especially those with advanced tumours.[5–7]

Based on few clinical trials and systematic reviews of the literature conducted in immunocompromised individuals,[8,9] international and national guidelines support using inactivated vaccines as potentially effective, minimally invasive, and generally well tolerated in patients with cancer, especially recommending vaccinations when haematological adverse events are expected from systemic therapies.[10–12]

On the other hand, few studies, mostly retrospective or case series, focused on selected cancer patient populations treated with non-immunosuppressive therapies, namely targeted agents and immune checkpoint inhibitors (ICI), which recently became the new standard of care in several advanced solid tumours.[13–17]

The INVIDIa-2 study was a multicenter prospective observational study designed to address the unmet need for counselling patients with advanced cancer receiving immune checkpoint inhibitors (ICI) regarding influenza vaccination. The primary results of the trial, describing the impact of vaccination on the incidence, severity, and lethality of influenza-like illness (ILI) in this population, were previously reported. The primary endpoint of the study was not met, with similar ILI incidence between vaccinated and non-vaccinated patients, but ILI complications, severity, and lethality were lower among vaccinated, with neglectable vaccine-related adverse events, definitely supporting a positive recommendation for influenza vaccination in patients with advanced cancer receiving immunotherapy.[18]

The study's secondary endpoints also included the outcome of patients receiving ICI according to the vaccine administration. The aim was to describe the potential impact of vaccination on the activity and efficacy

of immunotherapy and the disease history, irrespective of its antiviral effectiveness. Indeed, from the cancer therapy standpoint, we initially hypothesized that vaccination could interfere with the efficacy of ICI.[19] As these antibodies act by activating the CD8+ cytotoxic T cells, the interference of the vaccine, which triggers CD4+ T cell (T-helper)-mediated response, may be plausible concerning the cytokine-induced, cell-mediated immune interactions. The effect of introducing a new viral antigen, albeit inactivated, into the immune system of individuals treated with ICI is still unknown. According to the concept of "foreignness," viral antigens are thought to be more immunogenic than tumour antigens. They may divert T-cells response and potentially weaken antitumour response in favour of the antiviral reaction.[20–24] The efficacy of the cancer treatment could be reduced, especially if vaccination takes place during the early phase of ICI therapy before the immune response has been established.

Methods

Study design and participants

The INVIDIa-2 study was a multicenter prospective observational trial. The primary objective was to investigate the effectiveness of influenza vaccine administration in terms of the incidence and severity of ILI in patients with advanced cancer undergoing systemic treatment with ICI. Patients with advanced solid tumours candidates for therapy with ICI from October 1, 2019 to January 31, 2020 (corresponding to the influenza vaccinal season) were eligible for enrollment. Patients with ongoing ICI in this time-lapse were eligible to be provided they had started treatment no earlier than 1 April 2019 in order to exclude patients who were already receiving immunotherapy during the 2018–2019 vaccination season.

Local Institutional Review Board approval was required for each centre for inclusion in the study. Written informed consent was obtained for all the enrolled patients. All the study procedures were per the precepts of Good Clinical Practice and the declaration of Helsinki.

Procedures

Patients were enrolled between October 1, 2019 and January 31, 2020, and observed for vaccination and ILI until April 20, 2020. Their oncological outcome and survival were observed and recorded until November 12, 2021. Due to the observational nature of the study, the procedures were according to the clinical practice of the participating centres.

Outcomes

The study's primary endpoint was the time-adjusted ILI incidence, calculated in terms of time-to-ILI (TTI), from October 1, 2020 until April 30, 2020. The pre-specified study's secondary objectives regarded influenza vaccine safety during immunotherapy and the oncological outcome of patients receiving ICIs based on the vaccine administration or ILI occurrence. Detailed methods were reported in the original publication.[18] The sample size for this study was based on the primary analysis, and no specific calculation was made for this secondary analysis.

Secondary endpoints regarding the oncological outcome of patients were measured in terms of objective response rate (ORR), disease-control rate (DCR), progression-free survival (PFS), and overall survival (OS), the latter measured from ICI therapy start. The data cut-off for cancer treatment response assessment was July 31, 2020; the minimum follow-up forecasted for survival was 16 months. The vaccinated group was compared to the unvaccinated subjects, considering the distribution of patient characteristics in the two observational groups, as reported in the primary results.[18] Therefore, a propensity score analysis was performed to control differences in patient characteristics unbalanced between vaccinated and unvaccinated cohorts.

Statistical analysis

The propensity score matching was based on age, gender, smoking habits, primary tumour site, presence of comorbidities, and European Cooperative Oncology Group (ECOG) performance status (PS); the nneighboureighbor method with a ratio of 1:1 and a calliper of 0.2. The 'MatchIt' package was used for analysis.[25]

Survival curves were estimated using the Kaplan–Meier method, and differences between them were assessed with the log-rank test, and a Cox regression model was applied to adjust the vaccination effect on survival by known prognostic factors; Hazard Ratios (HR) and their 95% confidence intervals (95% CI) were reported. The same multivariable analysis for binary endpoints was performed using the regression logistic model, Odds Ratios (OR) and their 95% CI were reported.

The study reporting followed the STROBE guidelines.

Role of the funding source

The study funders had no role in the study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit the paper for publication. The corresponding author had full access to all the data in the study and had final responsibility for the publication.

Results

Patient characteristics

The INVIDIa-2 study prospectively enrolled 1279 advanced cancer patients receiving ICIs. Of them, 1188 were eligible for the primary analysis (Fig. 1), including

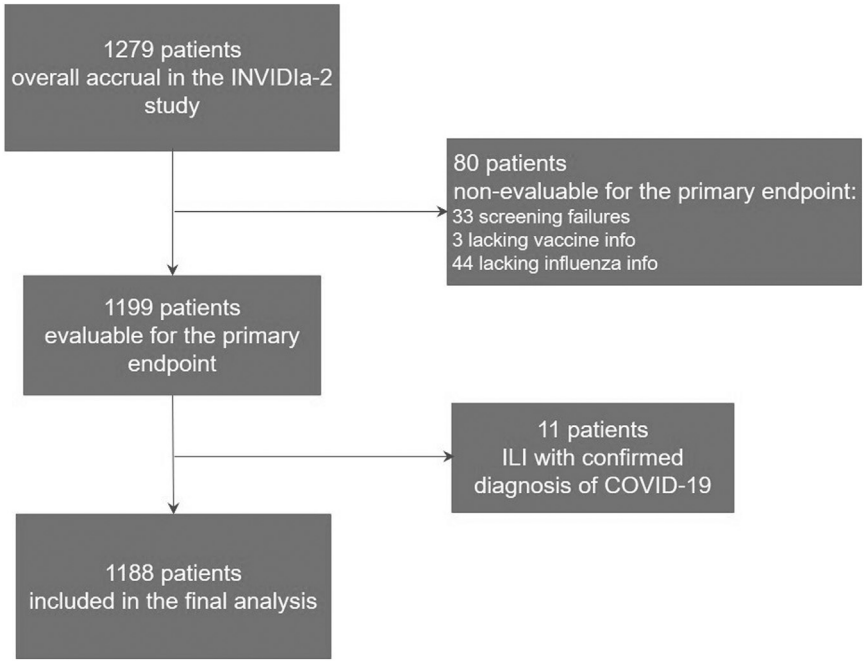

Fig. 1: **Patient disposition in the INVIDIa-2 study**.

581 patients (48.0%) vaccinated and 607 (51.1%) unvaccinated for influenza virus during the trial observation period.

The characteristics of the study population were reported in Table 1. The median time of exposure to ICI therapy at the time of the study accrual was 2 months (range 0–9). More details and the vaccine types administered to the study population were reported in the original publication. Herein, we reported previous data only if functional to the ICI outcome interpretation.

In the original study population, vaccinated patients were significantly more frequently elderly ($p < 0.0001$), males ($p = 0.004$), with poor (2 or 3) ECOG PS ($p = 0.009$), affected by lung cancer ($p = 0.01$), and by other non-cancer comorbidities ($p < 0.0001$) when compared to unvaccinated. The incidence of ILI in the overall study population was 98 cases (8.2%, 95% confidence interval CI 6.7–10.0). ILI lethality was 2% overall: 0/51 (0%) in vaccinated vs. 2/47 (4.3%) in unvaccinated patients.

The median follow-up for OS was of 20 months.

Outcome analyses

After a propensity score matching for age, sex, smoking habits, primary tumour site, comorbidity, and ECOG PS, 1004 patients were considered (N = 502 vaccinated and N = 502 unvaccinated) for the present analyses. Of them, 986 were evaluable for OS (N = 494 vaccinated and N = 492 unvaccinated). Covariates balance after PSM is always below 0.2 Standardized Mean Difference (Supplementary Figure S1).

Median OS (mOS) was significantly longer in vaccinated than unvaccinated patients ($p = 0.003$, Fig. 2), with 27.0 months (CI 19.5–34.6) vs. 20.9 months (16.6–25.2). The impact of vaccination on OS was heterogeneous across primary tumour subgroups, with clinically meaningful differences in the case of the lung (mOS 22.2 months in vaccinated vs. 18.3 months in unvaccinated) and kidney cancer (mOS not reached vs. 26.1 months) but not for patients with melanoma, head and neck, and other cancer types (Supplementary Figure S2).

When considering PFS, the impact of influenza vaccination was significant, with median PFS (mPFS) of 12.5 months (CI 10.4–14.6) for vaccinated vs. 9.6 months (CI 7.9–11.4) for unvaccinated patients ($p = 0.049$, Fig. 3 and Supplementary Figure S3). The vaccine's impact was also significant in terms of DCR, which was 74.7% in vaccinated vs. 66.5% in unvaccinated ($p = 0.005$), and there was only a trend for ORR, with 37.1% responding patients between vaccinated vs. 31.5% of unvaccinated ($p = 0.063$). Results for PFS, DCR, and ORR seem to be consistent within primary tumour subgroups (Supplementary Figures S3–S5).

Multivariable analyses

The results of the multivariable analyses of the population of patients included in the propensity score-

	Original population N = 1188	Vaccinated N = 581	Unvaccinated N = 607	PSM sample population N = 1004	Vaccinated N = 502	Unvaccinated N = 502
AGE (median, IQR, range)	69 (61–76), (20–93)	72 (64–77), (30–90)	66 (58–73), (20–93)	70 (62–76), (30–93)	71 (63–77), (30–90)	69 (62–75), (33–93)
Gender						
M	831 (69.9)	429 (73.8)	402 (66.2)	713 (71.0)	357 (71.1)	356 (70.9)
F	357 (30.1)	152 (26.2)	205 (33.8)	291 (29.0)	145 (28.9)	146 (29.1)
ECOG PS						
0	686 (57.7)	312 (53.7)	374 (61.6)	580	287	293
1	431 (36.3)	235 (40.4)	196 (32.3)	358	183	175
2	53 (4.5)	22 (3.8)	31 (5.1)	52	22	30
3	3 (0.3)	2 (0.3)	1 (0.2)	0	0	0
Unknown	15 (1.3)	10 (1.7)	5 (0.8)	14	10	4
Primary tumour						
Lung	645 (54.3)	337 (58.0)	308 (50.7)	580 (55.8)	282 (56.2)	278 (55.4)
RCC	201 (16.9)	107 (18.4)	94 (15.5)	168 (16.7)	94 (18.7)	74 (14.7)
Melanoma	153 (12.9)	52 (9.0)	101 (16.6)	119 (11.9)	45 (9.0)	74 (14.7)
UC	64 (5.4)	29 (5.0)	35 (5.8)	57 (5.7)	28 (5.6)	29 (5.8)
H&N	41 (3.5)	14 (2.4)	27 (4.4)	33 (3.3)	13 (2.6)	20 (4.0)
Other	84 (7.1)	42 (7.2)	42 (6.9)	67 (6.7)	40 (8.0)	27 (5.4)
ICI treatment line						
1	663 (55.8)	316 (54.4)	347 (57.2)	552 (55.0)	273 (54.4)	279 (55.6)
2	426 (35.9)	214 (36.8)	212 (34.9)	369 (36.7)	186 (37.0)	183 (36.5)
3	96 (8.0)	48 (8.3)	48 (7.9)	81 (8.1)	41 (8.2)	40 (8.0)
Unknown	3 (0.3)	3 (0.5)	0	2 (0.2)	2 (0.4)	0
Splenectomy						
Yes	8 (0.7)	5 (0.9)	3 (0.5)	8 (0.8)	5 (1.0)	3 (0.6)
No	915 (77.0)	455 (78.3)	460 (75.8)	776 (77.3)	385 (76.7)	391 (77.9)
Unknown	265 (22.3)	121 (20.8)	144 (23.7)	220 (21.9)	112 (22.3)	108 (21.5)
Therapy						
ICI/ICI + ICI	1075 (90.5)	527 (90.7)	548 (90.3)	917 (91.3)	454 (90.4)	463 (92.2)
ICI + Other*	113 (9.5)	54 (9.3)	59 (9.7)	87 (8.7)	48 (9.6)	39 (7.8)
Immunotherapy type						
Single agent (ICI)	1122 (94.4)	546 (94.0)	576 (94.9)	949 (94.5)	470 (93.6)	479 (95.4)
Combinations (ICI + ICI)	66 (5.6)	35 (6.0)	31 (5.1)	55 (5.5)	32 (6.4)	26 (5.2)
Comorbidity						
Yes	875 (73.7)	467 (86.4)	408 (67.2)	772 (76.9)	390 (77.7)	382 (76.1)
No	313 (26.3)	114 (19.6)	199 (32.8)	232 (23.1)	112 (22.3)	120 (23.9)
Comorbidity type						
Cardiovascular	202 (17.0)	118 (20.3)	84 (13.8)	177 (17.6)	96 (19.1)	81 (16.1)
Asthma/COPD	401 (33.8)	225 (38.7)	176 (29.0)	351 (35.0)	185 (36.9)	166 (33.1)
Diabetes	185 (15.6)	98 (16.9)	87 (14.3)	162 (16.1)	80 (15.9)	82 (16.3)
Others	283 (23.8)	143 (24.6)	140 (23.1)	253 (25.2)	123 (24.5)	130 (25.9)
Smoking habits						
Current	287 (24.2)	125 (21.5)	207 (34.1)	243 (24.2)	105 (20.9)	138 (27.5)
Former	512 (43.1)	288 (49.6)	224 (36.9)	441 (43.9)	243 (48.4)	198 (39.4)
Never	358 (30.1)	151 (26.0)	162 (26.7)	293 (29.2)	139 (27.7)	154 (30.7)
Unknown	31 (2.6)	17 (2.9)	14 (2.3)	27 (2.7)	15 (3.0)	12 (2.4)

IQR = interquartile range; ECOG PS = European Cooperative Oncology Group Performance Status; RCC = renal cell carcinoma; UC = urothelial cancer; H&N = head and neck carcinoma; ICI = immune checkpoint inhibitor; COPD = chronic obstructive pulmonary disease.

Table 1: **Characteristics of patients in the original study population and in the propensity score matched (PSM) sample used for the present analysis.**

matched (PSM) analysis are reported in Table 2, confirming the significant impact of influenza vaccination in terms of OS (HR 0.75, 95% C.I. 0.62–0.92; p = 0.005) and DCR (OR 1.47, 95% C.I. 1.11–1.96; p = 0.007).

Discussion

The original results of the INVIDIa-2 trial provided the recommendation in favour of influenza vaccination in patients with advanced cancer treated with ICI from the

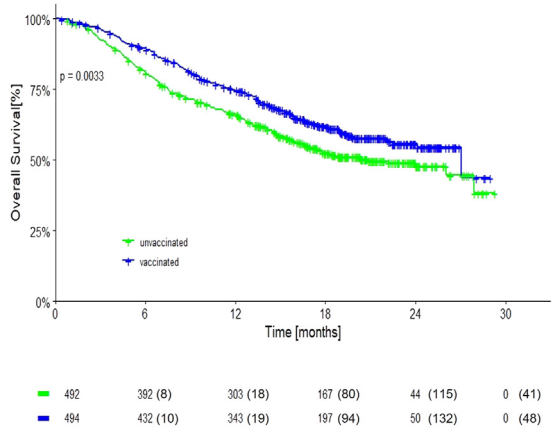

Fig. 2: **Overall survival of patients by vaccination status in the propensity-matched population.** (The numbers show the numbers at risk, and the numbers in brackets are the numbers censored).

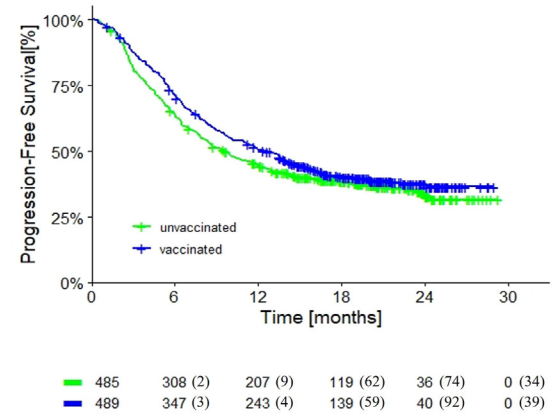

Fig. 3: **Progression-free survival of patients by vaccination status in the propensity-matched population.** (The numbers show the numbers at risk, and the numbers in brackets are the numbers censored).

anti-infectious standpoint.[18] Moreover, the study was also designed to uncover the possibility of an impact of the vaccine on the oncological outcome. The reason for this need was represented by the likeliness of interference between two different interventions on the immune system, namely the administration of ICI, stimulating the T cell-mediated response, and of viral antigens, also boosting cell-mediated immunity. In this context, it was crucial to rule out a negative impact of the vaccine on the ICI response.

The main limitation of the present analysis is the observational nature of the original study, leading to possible selection bias; moreover, the COVID-19 pandemic could have impacted the treatment outcomes, with a heterogeneity of cancer treatment continuity and survival follow-up. Further limitations are represented by the lack of biomarker correlates in the study population and the heterogeneity of the timing between ICI initiation and vaccination exposure.

Even considering these limitations, the present results not only exclude an unfavourable impact of influenza vaccination on the oncological outcome of patients to immunotherapy but also strongly suggest a synergy between the two immunogenic interventions. Indeed, vaccinated patients had a longer OS when compared to unvaccinated, even against the declared selection bias generated by the observational nature of the trial. The vaccinated population was affected by unfavourable selection bias, enriched with elderly and patients with multiple comorbidities, poor ECOG PS, and poor-prognosis primary malignancies (i.e., lung cancer). Nevertheless, this population had a mOS superior of 6 months to the unvaccinated group.

The positive impact on survival was not due to the antiviral effectiveness. Indeed, only two patients died as a consequence of ILI in the unvaccinated group, and the OS analysis had the same results when repeated without these two cases (data not shown). Moreover, the favourable impact was also confirmed regarding response to ICI, showing improved response (ORR and DCR) and PFS for vaccinated patients compared to unvaccinated. The effect of vaccination seems broadly consistent across tumour types for all outcomes considered.

The vaccination remained positively related to all the outcome endpoints at the multivariable analyses, as well as the ECOG PS, a well-recognized prognostic factor in the advanced cancer population.

These outstanding findings, despite being only hypothesis-generating in their observational context, not only further support a positive recommendation for influenza vaccination in this subset of cancer patients but even entice considering the administration of the vaccine as an immunological boost, likely able to improve the anti-tumour immune response during ICI.

In normal conditions, the vaccine stimulates both T and B cells, providing, first of all, protective humoral immunity. The involvement of the cellular response is likely limited. Nevertheless, the absence of mechanisms related to the regulation of T-cell activation, as during ICI therapy with the blockade of the crucial inhibitory checkpoint PD-1/PD-L1, the encounter with the viral antigen can lead to an overstimulation of T-cell-driven systemic inflammation.[19] The result could be an immune hyperactivation after influenza vaccination in patients treated with ICIs, with a consequent direct positive effect on anti-tumour immunity, as already suggested by the increase in OS in vaccine-or-virus-exposed subjects in our previous retrospective INVIDIa study.[14] This evidence is prospectively confirmed herein, even more robust, likely due to the only-positive impact of a split vaccinal antigen compared to its wild pathogenic counterpart.

Variables	OS HR (95% CI)	PFS HR (95% CI)	ORR OR (95% CI)	DCR OR (95% CI)
Vaccine	p = 0.005	p = 0.062	p = 0.08	p = 0.007
No	1.00	1.00	1.00	1.00
Yes	0.75 (0.62–0.92)	0.85 (0.72–1.01)	1.27 (0.97–1.67)	1.47 (1.11–1.96)
Sex	p = 0.46	p = 0.84	p = 0.92	p = 0.68
M	1.09 (0.87–1.36)	1.02 (0.85–1.23)	0.98 (0.72–1.34)	1.07 (0.78–1.47)
F	1.00	1.00	1.00	1.00
Age (in years)	1.0 (0.99–1.01) p = 0.53	1.00 (0.99–1.01) p = 0.50	1.0 (0.99–1.02) p = 0.66	1.01 (0.99–1.02) p = 0.24
ECOG PS	p < 0.0001	p < 0.0001	p = 0.025	p = 0.004
0	1.00	1.00	1.00	1.00
1–2	1.87 (1.53–2.29)	1.59 (1.34–1.88)	0.72 (0.55–0.96)	0.65 (0.49–0.87)
Smoking habits	p = 0.12	p = 0.16	p = 0.38	p = 0.28
Never	1.00	1.00	1.00	1.00
Former	0.76 (0.58–0.99)	0.82 (0.66–1.03)	1.24 (0.87–1.77)	1.35 (0.93–1.96)
Current	0.84 (0.63–1.12)	0.81 (0.63–1.04)	1.03 (0.68–1.54)	1.22 (0.81–1.84)
Tumour site	p < 0.0001	p = 0.001	p = 0.66	p = 0.31
Lung	1.62 (1.03–2.55)	1.54 (1.06–2.24)	0.67 (0.38–1.15)	0.59 (0.31–1.12)
RCC	0.97 (0.59–1.60)	1.31 (0.88–1.96)	0.65 (0.35–1.19)	0.75 (0.37–1.50)
Melanoma	0.85 (0.50–1.46)	0.80 (0.51–1.26)	0.84 (0.45–1.59)	0.79 (0.38–1.64)
UC	1.69 (0.94–3.04)	1.57 (0.96–2.57)	0.80 (0.38–1.70)	0.48 (0.21–1.10)
H&N	2.61 (1.38–4.91)	1.95 (1.12–3.38)	0.71 (0.28–1.79)	0.42 (0.16–1.11)
Others	1.00	1.00	1.00	1.00
Comorbidities	p = 0.73	p = 0.26	p = 0.41	p = 0.84
No	1.00	1.00	1.00	1.00
Yes	1.04 (0.82–1.34)	1.13 (0.92–1.39)	1.15 (0.83–1.61)	0.97 (0.68–1.36)

OS = overall survival; PFS = progression-free survival; ORR = objective response rate; DCR = disease control rate; HR = hazard ratio; OR = odds ratio; ECOG PS = European Cooperative Oncology Group performance status; RCC = renal cell carcinoma; UC = urothelial cancer; H&N = head and neck.

***Table 2*: Multivariable analyses for overall survival, progression-free survival, objective response rate, and disease control rate in the propensity score matched (PSM) sample.**

The mechanisms of the synergy between the vaccine and the anti-tumour immunity could involve pro-inflammatory cytokines stimulated by the anti-viral response, acting with a 'bystander' mechanism also against the anti-tumour response. The "Coley effect," a positive impact of bacterial antigens on the anti-tumour response observed more than two centuries ago, and the anti-tumour effect of the bacterial antigen Bacillus Calmette–Guerin against bladder cancer still currently used in clinical practice, are similar demonstrations of the bystander mechanism linking anti-infective and anti-tumour responses.[26,27]

One of the primary aims of the current immune-oncology research is to identify safe and effective immune adjuvants associated with ICI to stimulate anti-tumour immunity further. Nowadays, new compounds with complex mechanisms of action are being investigated for association with ICI, such as C-X-C chemokine receptor type 4 (CXCR4), poly (ADP-ribose) polymerase (PARP) or transforming growth factor (TGF)-β inhibitors. As a further alternative, tumour-associated antigens (TAAs) are being exploited to develop anti-cancer vaccines for immunotherapeutic combinations.[28]

The INVIDIa-2 trial final results, with the evidence of a better outcome of patients receiving ICI when the vaccine against influenza is administrated during anti-PD-1/PD-L1 immunotherapy, suggest boosting anti-tumour immunity can be likely far more straightforward than expected.

Contributors

MB: conceptualisation, study design, data collection, curation and interpretation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualisation, literature search, writing original draft, manuscript review & editing.

DG: data curation and interpretation, formal analysis, tables and figures, investigation, methodology, project administration, software, supervision, validation, manuscript review & editing.

AC, MDM, UDG, SB, SP: data interpretation, methodology, visualisation, manuscript review & editing.

MT: data collection and curation, funding acquisition, methodology, project administration, resources, software, supervision, validation, manuscript review & editing.

AC, ON: data collection and curation, project administration, resources, software, supervision, validation, visualisation, review & editing.

CP, EM, RL: funding acquisition, investigation, project administration, resources, software, supervision, validation, visualisation, review & editing.

All the other authors: data collection and interpretation, manuscript review & editing.

MB, DG, MT, and AC (all from the academic team) directly accessed and verified the underlying data reported in the manuscript. All authors confirm that they had full access to all the data in the study, approved the final manuscript, and accept responsibility for submitting it for publication.

Data sharing statement

The study protocol, the validation certificate for the eCRF platform, the statistical analysis plan, and the informed consent form of each patient included in the trial will be made available by the corresponding author upon request (melissa.bersanelli@gmail.com) at any time. Deidentified participants' data and the INVIDIa-2 study dataset will be available by the corresponding author upon reasonable request, to allow further analyses with the principal investigator's support, after approval of a proposal, and with a signed data access agreement.

Declaration of interests

The Federation of Italian Cooperative Oncology Groups (FICOG) received funding for the present study from Roche S.p.A. and Seqirus, and outside the present research from Astra Zeneca, Bristol-Myers Squibb (BMS), and Sanofi.

MB received funding for the present study from Roche S.p.A. and Seqirus (through FICOG as Institution, no personal fees). She also received, outside the current work: research funding from Pfizer and Novartis (through Institutions); honoraria as a speaker at scientific events (personal fees) by BMS, MSD, IPSEN, Novartis, Astra Zeneca, Pierre Fabre, and Pfizer; as a consultant for advisory role (personal fees) by IPSEN, Novartis, Sanofi, Pierre-Fabre, and Merck; personal fees for copyright transfer by Sciclone Pharmaceuticals, Pierre-Fabre, MSD, IPSEN, Pfizer, and Sanofi.

AC received speakers fees/grant consultancies from Astrazeneca, BMS, MSD, EISAI, IQVIA, and OncoC4.

UDG has served as a consultant for Astellas, Bayer, BMS, Ipsen, Janssen, Novartis, Pfizer, Sanofi, and Pharmamar; he received research funding from AstraZeneca, Roche, and Sanofi; and received travel funds from BMS, Ipsen, Janssen, Pfizer, and Roche during the conduct of the study.

MDM reports personal fees from Bristol Myers Squibb, personal fees from Merck Sharp & Dohme, personal fees from AstraZeneca, personal fees from Janssen, personal fees from Astellas, personal fees from Pfizer, personal fees from Eisai, personal fees from Takeda, grants from Tesaro GSK, outside the submitted work.

SB received honoraria as a speaker at scientific events and in advisory role by BMS, Pfizer; MSD, Ipsen, Roche S.p.A., Eli-Lilly, AstraZeneca, and Novartis; he also received research funding from Novartis.

VS participated, with personal fees, to advisory boards and speaker's bureaus for Roche S.p.A.

SC declared his role in an international board for Eli Lilly international.

AR declares Advisory Board activity for Bristol, Pfizer, Bayer, and Kyowa Kirin, and speaker honorarium from Roche Diagnostics.

PAZ reports outside the submitted work personal fees for advisory role, speaker engagements and travel and accommodation expenses from Merck Sharp & Dohme (MSD), Astellas, Janssen, Sanofi, Ipsen, Pfizer, Novartis, Bristol Meyer Squibb, Amgen, AstraZeneca, Roche, and Bayer.

MS received honoraria for advisory role from Janssen, and travel and accommodation expenses from Janssen, IPSEN, BMS, Astellas, and Pfizer.

ER had a role as consultant for MSD, Novartis, Pierre Fabre, Immunocore and Pfizer.

FG received personal fees from Eli Lilly, Roche, Boehringer Ingelheim, AstraZeneca, MSD, BMS, Pierre Fabre, Novartis, Merck, Takeda, Bayer, Novartis, and AMGEN for consulting activity; from Eli Lilly, Roche, Boehringer Ingelheim, AstraZeneca, BMS, AMGEN, MSD, Celgene, and Pierre Fabre for speakers bureaus.

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SP received honoraria as a speaker from Roche, Astra Zeneca, MSD, and GSK.

DG received honoraria as a speaker from Amgen.

MR received honoraria as speaker/consultant by MSD, Astra Zeneca, Bristol-MyersSquibb (BMS), Novartis, and Pfizer.

All the cited competing interests were outside the current work and not related to the content of our manuscript if not differently specified.

All remaining authors have declared no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.102044.

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