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Please cite this article as: Lin EP-Y, Huang L-C, Whisenant J, *et al*. Associations of influenza vaccination with severity of immune-related adverse events in patients with advanced thoracic cancers on immune checkpoint inhibitors. *ERJ Open Res* 2022; in press (https://doi.org/10.1183/23120541.00684-2021).

# Associations of Influenza Vaccination with Severity of Immune-Related Adverse Events in Patients with Advanced Thoracic Cancers on Immune Checkpoint Inhibitors

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**Keywords: Immune checkpoint inhibitor, Influenza vaccination, Immune-related adverse event**

**Take-Home Message**

Influenza vaccination does not increase toxicity for thoracic cancer patients on immune checkpoint inhibitors; is associated with a decreased risk for severe immune-related adverse events, and could be encouraged, especially in the covid-19 pandemic.

## Abstract

### Background

Whether influenza vaccination (FV) is associated with the severity of immune-related adverse events (IRAE) in patients with advanced thoracic cancer on immune checkpoint inhibitors (ICI) is not fully understood.

### Methods

Patients enrolled in this retrospective cohort study were identified from the Vanderbilt BioVU database and their medical records were reviewed. Patients with advanced thoracic cancer who received FV within 3 months prior to or during their ICI treatment period were enrolled in the FV-positive cohort and those who did not were enrolled in the FV-negative cohort. The primary objective was to detect whether FV is associated with decreased IRAE severity. The secondary objectives were to evaluate whether FV is associated with a decreased risk for grade 3-5 IRAE and better survival times. Multivariable ordinal logistic regression was used for primary analysis.

### Results

A total of 142 and 105 patients were enrolled in the FV-positive and FV-negative cohorts, respectively. There was no statistically significant difference in patient demographics or cumulative incidences of IRAE between the two cohorts. In the primary analysis, FV was inversely associated with the severity of IRAE (odds ratio=0.63; *P*= .046). In the secondary analysis, FV was associated with a decreased risk for grade 3-5 IRAE (odds ratio=0.42; *P*= .005). Multivariable Cox regression showed that FV was not associated with survival times.

## Conclusions

Our study showed that FV does not increase toxicity for patients with advanced thoracic cancer on ICI and is associated with a decreased risk for grade 3-5 IRAE. No statistically significant survival differences were found between patients with and without FV.

## Introduction

Patients with advanced thoracic cancer are at high risk of developing complications from infectious diseases, especially those frequently affecting the respiratory system, such as influenza and covid-19 (1). Influenza and covid-19 share common symptoms, such as fever, muscle ache, dyspnea, pneumonia, and acute respiratory distress syndrome (2). These two diseases can hardly be differentiated without molecular testing and their co-infections were reported (3).

Prior studies suggested high risk of influenza-related complications in cancer patients receiving cytotoxic chemotherapy, and vaccination as the primary protective strategy against influenza (1, 4-6). Accordingly, annual influenza vaccination (FV) for cancer patients is suggested by the guidelines of the Infectious Disease Society of America (IDSA), the National Comprehensive Cancer Network (NCCN), and the Advisory Committee on Immunization Practices (ACIP) (7-9). Consensus on FV for cancer patients receiving immune checkpoint inhibitors (ICI), however, has not been reached. This is partially attributed to the unpredictability of the occurrence and the severity of immune-related adverse events (IRAE) relevant to ICI treatment. A recently published multicenter prospective observational study (INVIDIa-2) showed significantly less influenza-like illness in cancer patients on ICI with FV. The INVIFIa-2 study results, therefore, supported the recommendation for FV in patients with advanced cancers on ICI based on the overall reduction of influenza-relevant complications (10). This study, however, did not discuss the association of FV with IRAE. While three prior studies and a systemic review showed no evidence of increased IRAE incidence among cancer patients receiving FV when they were on ICI, one study showed the opposite results (11-15). In addition, data on the associations of FV with IRAE severity in thoracic cancer patients is lacking.

In the covid-19 pandemic, FV is more important than ever. As ICI is taking an increasingly central role in thoracic oncology, it is of particular importance to get a better insight into this issue to decipher whether FV should be encouraged in this patient population. The primary objective of this study was to detect whether FV is associated with decreased IRAE severity. The secondary objectives were to evaluate whether FV is associated with a decreased risk for grade 3-5 IRAE and better survival times.

## Method

### Data Source, Study Population and Objectives

Patients enrolled in this retrospective cohort study were identified from the Vanderbilt BioVU database through programmer data pull followed by manual review of the electronic medical records (EMR). Vanderbilt BioVU is a de-identified EMR-based biorepository that enables longitudinal EMR study and paired genetic data assessment. All data collected were de-identified and the study was approved by the institutional review board (IRB) (Vanderbilt University Medical Center IRB #190712) according to principles of the Declaration of Helsinki.

Patients who fulfilled the diagnostic codes of International Classification of Disease, $9^{th}$ or $10^{th}$ Revision, Clinical Modification (ICD-9-CM or ICD-10-CM) for lung cancer, malignant mesothelioma, or thymic cancer (ICD-9-CM 162.0-163.9, ICD-10-CM C33-34 and C37-38) and received at least one dose of ICI between July 2012 and December 2018 were identified. The cutoff date of data pull was October 25, 2019. The medical records of the identified subjects were manually reviewed. Only those who fulfilled the inclusion criteria confirmed by the manual review were enrolled. Patients who received FV during or within 3 months prior to their ICI treatment period were subgrouped to the FV-positive cohort and those who did not were subgrouped to the FV-negative cohort.

The primary objective of this study was to detect whether FV is associated with decreased IRAE severity. The secondary objectives were to evaluate whether FV is associated with a decreased risk for grade 3-5 IRAE and better survival times, i.e., progression-free survival (PFS) and overall survival (OS).

### Definitions

The ICIs used in the study population included PD-1 inhibitors (nivolumab or pembrolizumab), PD-L1 inhibitors (atezolizumab or durvalumab) and CTLA-4 inhibitors (ipilimumab or tremelimumab). If a therapeutic regimen included a single ICI, it is categorized based on the ICI given.

For example, when the regimen is pembrolizumab plus chemotherapy, then it is categorized into the pembrolizumab group. If a regimen included two ICIs, for example ipilimumab plus nivolumab or tremelimumab plus durvalumab, it is categorized into the CTLA-4 combination group. Two types of influenza vaccines were used in the study cohort: (1) standard-dose quadrivalent influenza vaccine, and (2) quadrivalent high-dose influenza vaccine.

The ICI treatment responses were defined as stable disease (SD), partial response (PR), complete response (CR), or progressive disease (PD) based on the RECIST 1.1 criteria (Response Evaluation Criteria in Solid Tumors) (16). Severity of IRAE was defined per Common Terminology Criteria for Adverse Events version 5.0 (CTCAE version 5.0) (17). PFS was defined as the number of months between the date of first ICI administration to the date of first disease progression following ICI treatment or the date of death, whichever came first. OS was defined as the number of months between the date of first ICI administration to the date of death. Patients with no event observed were censored at the last follow-up date. Types of comorbidity among the study subjects were listed in the appendix.

**Exposures and Outcome Measurement**

The treatment exposure was recorded as binary for FV (positive vs negative). The severity of IRAE was recorded as no IRAE or grade 1-5 IRAE per CTCAE version 5.0 (17). The primary outcome was the severity of IRAE. The secondary outcomes included grade 3-5 IRAE (Yes [i.e., grade 3-5 IRAE] vs No [i.e., grade 1-2 IRAE and no IRAE]), PFS and OS. Patients were separated into subgroups for additional analysis for IRAE (grade 3-5 IRAE vs no IRAE).

**Statistical analysis**

The primary objective of this study was to evaluate whether FV is associated with decreased IRAE severity. The null hypothesis for the primary outcome is that FV will increase or has no impact

on the severity of IRAE, and the alternative hypothesis is that FV will decrease the severity of IRAE. The secondary objectives were to evaluate whether FV is associated with decreased IRAE severity and better PFS and OS. The null hypotheses for the secondary outcomes were that FV is associated with an increased risk for grade 3-5 IRAE and poorer PFS and OS, or has no impact on the severity of IRAE and survival times. The alternative hypotheses were that FV is associated with a decreased risk for grade 3-5 IRAE and better PFS and OS.

The study sample size was determined using precision analysis (Appendix: precision analysis). With a proposed sample size of 247 (FV-positive = 142, FV-negative = 105), the half-width of the 90% confidence interval of the estimated odds ratio is less than 0.28. Therefore, it is reassured that our study has excellent precision of the reported results.

Multiple imputations for missing values using chained equations were first carried out. To improve the balance of covariate distribution between the FV-positive and the FV-negative cohorts, propensity score matching (PSM) using the nearest-neighbor method with a 1:1 ratio without caliper was then applied and the following factors were adjusted: age, race, gender, smoking status, trial patients or not, ICI type received, cardiovascular comorbidities, pulmonary comorbidities, second primary cancers, metabolic comorbidities, autoimmune comorbidities, and other comorbidities (defined as renal, cerebrovascular or neurological comorbidities).

The primary analysis was done with the ordinal logistic regression and included 7 pre-determined variables: FV status, race, gender, smoking status, age, trial patients or not, and types of ICI received. Goodness of fit was assessed by the Harrell's C-statistics (18). The logistic regression was used for secondary analysis and 7 pre-determined covariates were adjusted: FV status, race, gender, smoking status, age, trial patients or not, and types of ICI received. The survival curves were estimated by the Kaplan-Meier method and the differences were compared by the Cox regression for the time-to-event outcomes. The subgroup analysis was done with the logistic regression and adjusted for FV status, race, gender, smoking status, age, trial patients or not, and types of ICI received. The adjusted

odds ratios (ORs) or hazard ratios (HRs) with 90% confidence intervals (CIs) were reported. Methods for sensitivity analyses were shown in the Appendix.

Descriptive statistics was used to display the demographic information of the participants. Differences between the cohorts were compared with $\chi 2$ test for categorical variables and with Wilcoxon rank sum test for continuous variables. Elastic-net and horseshoe regression analysis were used to validate the consistency and robustness of the estimated FV effect. Statistical significance was present as one-sided $\alpha = 0.05$. All data analyses were performed using base R 4.0 (R Foundation, Vienna, Austria) and the R packages rms, MatchIt, Hmisc, survival, survminer, MASS, glmnet and bayesreg (19-23).

## Results

### *Patient characteristics*

A total of 247 patients were included in the analysis. There were 142 patients in the FV-positive cohort and 105 patients in the FV-negative cohort. For the patients in the FV-positive cohort, 91% (n=129) were white, 51% (n=72) were male, 89% (n=126) were ever smokers, and 67% (n=95) had the cancer diagnosed at age more than 60 years. For the patients in the FV-negative cohort, 90% (n=95) were white, 56% (n=59) were male, 93% (n=98) were ever smokers, and 70% (n=74) had the cancer diagnosed at age more than 60 years. One percent (n=2) or 3% (n=3) of the patients had influenza prodromes (fever, rigor, or myalgia) in the FV-positive or the FV-negative cohort, respectively, and 1% (n=1) of the patients in each group was admitted due to influenza-related complications.

All the patients had locally advanced or metastatic thoracic cancer. The most common cancer type in both cohorts was non-small cell lung cancer (NSCLC). For patients in the FV-positive cohort, 87% (n=124) had NSCLC; 7% (n=10) had small cell lung cancer (SCLC); 2% (n=3) had mixed NSCLC and SCLC, and 4% (n=5) had malignant mesothelioma (n=4) or thymic cancer (n=1). For patients in the FV-negative cohort, 82% (n=86) had NSCLC; 15% (n=16) had SCLC; 2% (n=2) had mixed NSCLC and SCLC, and 1% (n=1) had thymic cancer.

In the FV-positive cohort, 78% (n=111) of the patients received a PD-1 inhibitor (nivolumab or pembrolizumab); 13% (n=19) received a PD-L1 inhibitor (atezolizumab or durvalumab); 2% (n=3) had ipilimumab monotherapy, and 6% (n=9) had CTLA-4 combination therapy (ipilimumab plus nivolumab). In the FV-negative cohort, 77% (n=81) of the patients received a PD-1 inhibitor (nivolumab or pembrolizumab); 10% (n=11) received a PD-L1 inhibitor (atezolizumab or durvalumab); 12% (n=13) had CTLA-4 combination therapy (ipilimumab plus nivolumab or tremelimumab plus durvalumab). There was no statistically significant difference in cumulative incidences among these basic demographic features, types and numbers of comorbidities, disease stages or cell types, and types or routes of ICI received between the two cohorts both before and after PSM (Table 1, all $P > .05$).

The median time interval between the first dose of ICI and the occurrence of IRAE was 5.2 (IQR: 3.0 to 7.0) months in the FV-positive cohort and 2.9 (IQR: 1.4 to 6.8) months in the FV-negative cohort. The cumulative incidences of IRAE were not of statistically significant difference between the two cohorts — FV-positive cohort, 47%, n=67; FV-negative cohort, 52%, n=55 ($P$ = .42). However, among all the IRAE events, there was a trend towards a higher likelihood of pneumonitis (17% vs. 12%), myocarditis (4% vs. 1%), and neuromuscular complications (10% vs. 3%) in the FV-negative cohort compared to the FV-positive cohort.

The cumulative incidence of grade 3-5 IRAE was lower in the FV-positive cohort than in the FV-negative cohort (20%, n=29 and 37%, n=39, respectively; $P$ = .004). There were 23% (n=32) or 39% (n=41) of the patients required immunosuppressive agents for the control of IRAE in the FV-positive or the FV-negative cohort, respectively ($P$ = .005). ICIs were permanently discontinued due to IRAE among 18% (n=25) of the patients in the FV-positive cohort and 30% (n=32) of the patients in the FV-negative cohort ($P$ = .018). As shown in the table 2, the trends were similar before and after PSM. Moreover, despite statistically nonsignificant, there was a higher likelihood of IRAE development during the influenza season (fall and winter) than outside the influenza season (spring and summer) in the FV-negative cohort (55% vs 45%) (Table 3).

***Influenza vaccination is associated with a decreased severity of IRAEs but not overall survival***

We first investigated whether FV is associated with decreased severity of IRAE. In the main analysis, a PSM matching ratio of 1:1 without caliper was applied (n=105 in each cohort). The ordinal logistic regression showed an inverse association between FV and the severity of IRAE (OR, 63; $P$ = .046) (Table 4). In the secondary analysis, the logistic regression showed that FV was associated with a decreased risk for grade 3-5 IRAE (OR, 0.42; $P$ = .005) (Table 5). In the subgroup analysis, when only subjects with no IRAE and grade 3-5 IRAE were included, the results revealed that FV was associated with a decreased risk for grade 3-5 IRAE (OR, 0.46; $P$ = .016) (Table 6). Similar results

were shown by the additional analyses (Appendix: sensitivity analysis I & II, eTable 3-5 and eTable 7-9).

We next investigated whether FV is associated with better survival times. The median PFS times were 6.55 or 5.32 months and the median OS times were 12.7 or 12.2 months for the FV-positive or the FV-negative cohort, respectively. Multivariable Cox regression showed that FV was not associated with PFS (HR, 0.96; *P* = .395) or OS (HR, 1.06, *P* = .371) (Table 7 and Appendix eFigure 3). Similar results were revealed in the additional analyses (Appendix: sensitivity analysis I & II, eTable 6 and eTable 10).

## Discussion

This study investigated associations between FV and the risks of IRAE among thoracic cancer patients on ICI. The treatment regimens were not restricted to a single PD-1 inhibitor, but included PD-1, PD-L1, or CTLA-4 inhibitors, and their combinations, reflecting real practice. There was no statistically significant difference in the IRAE cumulative incidence between the FV-positive and the FV-negative cohorts. In the primary analysis, we showed an inverse association between FV and the severity of IRAE. In the secondary analyses, the data further indicated a statistically significant inverse association between FV and the development of grade 3-5 IRAE while no association between FV and survival times was revealed. The subgroup analysis also suggested a decreased risk for grade 3-5 IRAE in the FV-positive cohort. The results implicate potential benefits of FV for patients with advanced-stage thoracic cancer on ICI therapy.

The cumulative incidence of overall IRAE (49%) observed in our study was higher than those reported in the prior studies (24-28). This could be partly explained by the fact that ICI included in our study was not restricted to a single PD-1/PD-L1 axis inhibitor. Consistent with the data from the prior studies, the most frequently observed IRAE in our study population was endocrinopathy (17%), and dermatological adverse events (10%) as well as hepatitis/colitis (10%) were also ranked in the top five. A distinct feature observed here is the high cumulative incidence of pneumonitis (14%). Nevertheless, although the incidence of pneumonitis observed here is higher than those reported in the clinical trial settings (3%-5%) (25-26), it is close to the numbers reported in the real-world datasets, including a cohort with 205 ICI-treated NSCLC patients (19%) (29) and a cohort with 91 PD-1/PD-L1 inhibitor-treated NSCLC patients (10%) (24).

Of note, the incidence of pneumonitis is higher in the FV-negative cohort than in the FV-positive cohort. The same trend was also observed with neuromuscular complications and myocarditis. Pneumonitis, severe neuromuscular complications and myocarditis are potential lethal IRAEs that deserve special attention. In our primary and secondary analyses, we showed inverse associations

between FV and the severity of IRAE. In the subgroup analysis, a significant increased risk for severe IRAE was revealed in the FV-negative cohort. These results suggested a potential protective effect of FV for severe IRAE. In line with our findings, a recent study also reported reduced risks for major adverse cardiac events among patients on ICI and FV who developed myocarditis (30).

Remarkably, despite without statistical significance, there was a trend toward a higher IRAE incidence during the influenza season (fall and winter) than outside the influenza season (spring and summer) in the FV-negative cohort. Importantly, pulmonary complications are not uncommon upon influenza infection, and influenza-related neuronal and cardiac complications can be fatal (31-32). With the retrospective nature of the current study, incidence of influenza might be underestimated, especially in the FV-negative cohort, and so as to the influenza-relevant complications. According to the INVIDIa-2 study, FV significantly reduced influenza-like illness in patients with advanced cancer on ICIs (10). The results of INVIDIa-2 study suggested favorable outcomes with FV for patients on ICIs. The phenomenon observed was not quite the same as it was among cancer patients on chemotherapy, with which the suppressed host immunity might impede the generation of satisfactory antibody level in response to FV. Despite the fact, FV is still recommended for cancer patients on chemotherapy as it stands as the most practical way for influenza prevention. It is plausible that among cancer patients on ICIs, FV reduces severe inflammatory complications on major organs, both due to the infection itself or the interaction between infection and drug-induced inflammatory responses. Taken together, the benefit of FV may outweigh its risk for patients with advanced thoracic cancer on ICI both from the IRAE and influenza-related complication point of views.

This study is limited by the lack of randomization and missing variables are inevitable due to its retrospective nature. While adjustments and varying methodological techniques were applied, residual confounding may affect the results. Nevertheless, this is the largest cohort study investigating safety of FV in patients with advanced thoracic cancer on ICI. Furthermore, all the study subjects were

enrolled from a single institute with high-quality de-identified EMR and low loss-to-follow-up rate. These advantages facilitated comprehensive data collection.

In summary, our study suggests that FV does not increase toxicity for patients with advanced thoracic cancer on ICI and FV is associated with a decreased risk for severe IRAE. Taken together, FV may be recommended for this patient population.

**Acknowledgement**

The dataset(s) used for the analyses described were obtained from Vanderbilt University Medical Center's BioVU which is supported by numerous sources: institutional funding, private agencies, and federal grants. These include the NIH funded Shared Instrumentation Grant S10RR025141; and CTSA grants UL1TR002243, UL1TR000445, and UL1RR024975.

**Funding**

This work was supported by the National Institutes of Health [P30CA068485, U24CA163056, U24CA213274, P50CA236733, P50CA098131, U54CA163072], Ministry of Science and Technology Taiwan [MOST107-2314-B-002-231, MOST108-2314-B-030-014, MOST109-2314-B-038-150, MOST108-2314-B-002-197-MY2], National Health Research Institute Taiwan [NHRI-EX109-10937BC], and Taipei Medical University and Hospital [DP5-111-21314-07, TMU110-AE1-B13, 110TMU-TMUH-02-5].

**Conflict of Interest:**

Leora Horn: employee of AstraZeneca

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**Table 1.** Demographic features of the study cohorts

| | Before Propensity Score Matching | | | | | After Propensity Score Matching† | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **N** | **FV-Positive** (N=142) | **FV-Negative** (N=105) | **Combined** (N=247) | **P-value** | **N** | **FV-Positive** (N=105) | **FV-Negative** (N=105) | **Combined** (N=210) | **P-value** |
| **Race, No. (%)** | 247 | | | | 0.921 | 210 | | | | 0.448 |
| White | | 129 (91%) | 95 (90%) | 224 (91%) | | | 98 (93%) | 95 (90%) | 193 (92%) | |
| Non-White | | 13 ( 9%) | 10 (10%) | 23 ( 9%) | | | 7 ( 7%) | 10 (10%) | 17 ( 8%) | |
| **Gender, No. (%)** | 247 | | | | 0.393 | 210 | | | | 0.889 |
| Male | | 72 (51%) | 59 (56%) | 131 (53%) | | | 60 (57%) | 59 (56%) | 119 (57%) | |
| Female | | 70 (49%) | 46 (44%) | 116 (47%) | | | 45 (43%) | 46 (44%) | 91 (43%) | |
| **Age, No. (%)** | 247 | | | | 0.550 | 210 | | | | 0.537 |
| < 60 | | 47 (33%) | 31 (30%) | 78 (32%) | | | 27 (26%) | 31 (30%) | 58 (28%) | |
| ≥ 60 | | 95 (67%) | 74 (70%) | 169 (68%) | | | 78 (74%) | 74 (70%) | 152 (72%) | |
| **Smoking status, No. (%)** | 247 | | | | 0.219 | 210 | | | | 1 |
| Ever smoker | | 126 (89%) | 98 (93%) | 224 (91%) | | | 98 (93%) | 98 (93%) | 196 (93%) | |
| Never smoker | | 16 (11%) | 7 ( 7%) | 23 ( 9%) | | | 7 ( 7%) | 7 ( 7%) | 14 ( 7%) | |
| **Cancer type*, No. (%)** | 247 | | | | 0.126 | 210 | | | | 0.260 |
| NSCLC | | 124 (87%) | 86 (82%) | 210 (85%) | | | 89 (85%) | 86 (82%) | 175 (83%) | |
| SCLC | | 10 ( 7%) | 16 (15%) | 26 (11%) | | | 9 ( 9%) | 16 (15%) | 25 (12%) | |
| NSCLC/SCLC | | 3 ( 2%) | 2 ( 2%) | 5 ( 2%) | | | 3 ( 3%) | 2 ( 2%) | 5 ( 2%) | |
| Others | | 5 ( 4%) | 1 ( 1%) | 6 ( 2%) | | | 4 ( 4%) | 1 ( 1%) | 5 ( 2%) | |
| Malignant mesothelioma | | 4 (3%) | 0 (0%) | 4 (2%) | | | 4 (4%) | 0 (0%) | 4 (2%) | |
| Thymic cancer | | 1 (1%) | 1 (1%) | 2 (1%) | | | 0 (0%) | 1 (1%) | 1 (0%) | |
| **Stages, No. (%)** | 247 | | | | 0.479 | 210 | | | | 1 |
| Stage III | | 13 ( 9%) | 7 ( 7%) | 20 ( 8%) | | | 7 ( 7%) | 7 ( 7%) | 14 ( 7%) | |
| Stage IV | | 129 (91%) | 98 (93%) | 227 (92%) | | | 98 (93%) | 98 (93%) | 196 (93%) | |
| **Trial patients, No. (%)** | 247 | | | | 0.326 | 210 | | | | 0.471 |
| Yes | | 56 (39%) | 35 (33%) | 91 (37%) | | | 40 (38%) | 35 (33%) | 75 (36%) | |
| No | | 86 (61%) | 70 (67%) | 156 (63%) | | | 65 (62%) | 70 (67%) | 135 (64%) | |
| **ICI received †, No. (%)** | 247 | | | | 0.163 | 210 | | | | 0.284 |
| PD-1 inhibitor | | 111 (78%) | 81 (77%) | 192 (78%) | | | 83 (79%) | 81 (77%) | 164 (78%) | |
| PD-L1 inhibitor | | 19 (13%) | 11 (10%) | 30 (12%) | | | 10 (10%) | 11 (10%) | 21 (10%) | |
| CTLA-4 inhibitor | | 3 ( 2%) | 0 ( 0%) | 3 ( 1%) | | | 3 ( 3%) | 0 ( 0%) | 3 ( 1%) | |
| CTLA-4 combination | | 9 ( 6%) | 13 (12%) | 22 ( 9%) | | | 9 ( 9%) | 13 (12%) | 22 (10%) | |
| **Best ICI response, No. (%)** | 247 | | | | 0.396 | 210 | | | | 0.474 |
| PD | | 48 (34%) | 41 (39%) | 89 (36%) | | | 36 (34%) | 41 (39%) | 77 (37%) | |
| Responses other than PD | | 94 (66%) | 64 (61%) | 158 (64%) | | | 69 (66%) | 64 (61%) | 133 (63%) | |
| **Number of Comorbidities, No. (%)** | 234 | | | | 0.905 | 210 | | | | 0.719 |
| 0 | | 2 ( 2%) | 1 ( 1%) | 3 ( 1%) | | | 3 ( 3%) | 1 ( 1%) | 4 ( 2%) | |
| 1 | | 39 (30%) | 29 (28%) | 68 (29%) | | | 33 (31%) | 30 (29%) | 63 (30%) | |
| 2 | | 33 (25%) | 30 (29%) | 63 (27%) | | | 28 (27%) | 31 (30%) | 59 (28%) | |
| 3 and above | | 57 (44%) | 43 (42%) | 100 (43%) | | | 41 (39%) | 43 (41%) | 84 (40%) | |
| **Comorbidity, No. (%)** | | | | | | | | | | |
| Cardiovascular | 234 | 85 (65%) | 68 (66%) | 153 (65%) | 0.856 | 210 | 68 (65%) | 69 (66%) | 137 (65%) | 0.885 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Pulmonary | 234 | 53 (40%) | 50 (49%) | 103 (44%) | 0.216 | 210 | 50 (48%) | 50 (48%) | 100 (48%) | 1 |
| Metabolic | 234 | 53 (40%) | 47 (46%) | 100 (43%) | 0.427 | 210 | 43 (41%) | 47 (45%) | 90 (43%) | 0.577 |
| Second primary cancers | 234 | 34 (26%) | 17 (17%) | 51 (22%) | 0.082 | 210 | 18 (17%) | 17 (16%) | 35 (17%) | 0.853 |
| Autoimmune | 234 | 25 (19%) | 27 (26%) | 52 (22%) | 0.193 | 210 | 23 (22%) | 28 (27%) | 51 (24%) | 0.421 |
| Nephrology/Urology | 234 | 16 (12%) | 15 (15%) | 31 (13%) | 0.599 | 204 | 11 (11%) | 15 (15%) | 26 (13%) | 0.432 |
| Cerebrovascular | 234 | 13 (10%) | 11 (11%) | 24 (10%) | 0.850 | 204 | 8 ( 8%) | 11 (11%) | 19 ( 9%) | 0.498 |
| Neurological | 234 | 6 ( 5%) | 8 ( 8%) | 14 ( 6%) | 0.308 | 204 | 4 ( 4%) | 8 ( 8%) | 12 ( 6%) | 0.248 |
| **Flu Prodromes, No. (%)** | 247 | | | | 0.830 | 210 | | | | 0.313 |
| Yes | | 2 ( 1%) | 3 ( 3%) | 5 ( 2%) | | | 1 ( 1%) | 3 ( 3%) | 4 ( 2%) | |
| No | | 140 (99%) | 102 (97%) | 242 (98%) | | | 104 (99%) | 102 (97%) | 206 (98%) | |
| **Flu-related Hospitalization, No. (%)** | 247 | | | | 0.419 | 210 | | | | 0.316 |
| Yes | | 1 ( 1%) | 1 ( 1%) | 2 ( 1%) | | | 0 ( 0%) | 1 ( 1%) | 1 ( 0%) | |
| No | | 141 (99%) | 104 (99%) | 245 (99%) | | | 105 (100%) | 104 ( 99%) | 209 (100%) | |

Note: * Cancer type: NSCLC: non-small cell lung cancer; SCLC: small cell lung cancer; NSCLC/SCLC: mixed non-small cell lung cancer and small cell lung cancer; Others: malignant mesothelioma or thymic cancer; † PD-1 inhibitors include nivolumab and pembrolizumab; PD-L1 inhibitors include atezolizumab and durvalumab; CTLA-4 inhibitor here indicates ipilimumab; CTLA-4 combinations include ipilimumab plus nivolumab and tremelimumab plus durvalumab.

† One of the five PSM model runs after multiple imputations; numbers change very slightly among 5 runs.

**Table 2.** Immune-related adverse events (IRAE) in the study cohorts

| | | Before Propensity Score Matching | | | | | After Propensity Score Matching† | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **N** | **FV-Positive** (N=142) | **FV-Negative** (N=105) | **Combined** (N=247) | **P-value** | **N** | **FV-Positive** (N=105) | **FV-Negative** (N=105) | **Combined** (N=210) | **P-value** |
| **IRAE, No. (%)** | 247 | | | | 0.419 | 210 | | | | 0.49 |
| Yes | | 67 (47%) | 55 (52%) | 122 (49%) | | | 50 (48%) | 55 (52%) | 105 (50%) | |
| No | | 75 (53%) | 50 (48%) | 125 (51%) | | | 55 (52%) | 50 (48%) | 105 (50%) | |
| **IRAE severity grading, No. (%)** | 247 | | | | **0.004** | 210 | | | | **0.004** |
| Grade 5 | | 1 (1%) | 0 (0%) | 1 (0%) | | | 1 (1%) | 0 (0%) | 1 (0%) | |
| Grade 4 | | 2 (1%) | 1 (1%) | 3 (1%) | | | 1 (1%) | 1 (1%) | 2 (1%) | |
| Grade 3 | | 26 (18%) | 38 (36%) | 64 (26%) | | | 18 (17%) | 38 (36%) | 56 (27%) | |
| Grade 2 | | 27 (19%) | 16 (15%) | 43 (17%) | | | 22 (21%) | 16 (15%) | 38 (18%) | |
| Grade 1 | | 11 (8%) | 0 (0%) | 11 (4%) | | | 8 (8%) | 0 (0%) | 8 (4%) | |
| No IRAE | | 75 (53%) | 50 (48%) | 125 (51%) | | | 55 (52%) | 50 (48%) | 105 (50%) | |
| **IRAE, No. (%)** | 247 | | | | **0.006** | 210 | | | | **0.005** |
| Grade 3-5 | | 29 (20%) | 39 (37%) | 68 (28%) | | | 20 (19%) | 39 (37%) | 59 (28%) | |
| Grade 1-2 | | 38 (27%) | 16 (15%) | 54 (22%) | | | 30 (29%) | 16 (15%) | 46 (22%) | |
| No IRAE | | 75 (53%) | 50 (48%) | 125 (50%) | | | 55 (52%) | 50 (48%) | 105 (50%) | |
| **IRAE Type, No. (%)** | | | | | | | | | | |
| Endocrinopathy | 247 | 27[+] (19%) | 16[#] (15%) | 43 (17%) | 0.440 | 210 | 22[&] (21%) | 16[^] (15%) | 38 (18%) | 0.282 |
| Hypothyroidism | | 21 (15%) | 12 (11%) | 33 (13%) | | | 17 (16%) | 12 (11%) | 29 (28%) | |
| Adrenal insufficiency | | 8 (6%) | 4 (4%) | 12 (5%) | | | 6 (6%) | 4 (4%) | 10 (10%) | |
| Hypophysitis | | 1 (1%) | 1 (1%) | 2 (1%) | | | 1 (1%) | 1 (1%) | 2 (2%) | |
| Pneumonitis | 247 | 17 (12%) | 18 (17%) | 35 (14%) | 0.250 | 210 | 12 (11%) | 18 (17%) | 30 (14%) | 0.237 |
| Dermatological | 247 | 17 (12%) | 7 (7%) | 24 (10%) | 0.160 | 210 | 14 (13%) | 7 ( 7%) | 21 (10%) | 0.107 |
| Hepatitis/Colitis | 247 | 16 (11%) | 8 (8%) | 24 (10%) | 0.340 | 210 | 8 ( 8%) | 8 ( 8%) | 16 ( 8%) | 1 |
| Hepatitis | | 9 (6%) | 6 (6%) | 15 (6%) | | | 5 (5%) | 6 (6%) | 11 (5%) | |
| Colitis | | 7 (5%) | 2 (2%) | 9 (4%) | | | 3 (3%) | 2 (2%) | 5 (2%) | |
| Neuromuscular | 247 | 5 ( 3%) | 10 (10%) | 15 (6%) | 0.051 | 210 | 4 ( 4%) | 10 (10%) | 14 ( 7%) | 0.097 |
| Severe fatigue | 247 | 4 ( 3%) | 4 ( 4%) | 8 ( 3%) | 0.660 | 210 | 3 ( 3%) | 4 ( 4%) | 7 ( 3%) | 0.701 |
| Myocarditis | 247 | 1 ( 1%) | 4 ( 4%) | 5 ( 2%) | 0.087 | 210 | 1 ( 1%) | 4 ( 4%) | 5 ( 2%) | 0.174 |
| Hematological | 247 | 0 ( 0%) | 2 ( 2%) | 2 ( 2%) | 1 | 210 | 0 ( 0%) | 2 ( 2%) | 2 ( 1%) | 0.155 |
| Nephritis | 247 | 1 ( 1%) | 0 ( 0%) | 1 ( 0%) | 0.390 | 210 | 1 ( 1%) | 0 ( 0%) | 1 ( 0%) | 0.316 |
| **Immunosuppressive agents for IRAE No. (%)** | 247 | | | | **0.005** | 210 | | | | **0.004** |
| Yes | | 32 (23%) | 41 (39%) | 73 (30%) | | | 22 (21%) | 41 (39%) | 63 (30%) | |
| No | | 110 (77%) | 64 (61%) | 174 (70%) | | | 83 (79%) | 64 (61%) | 147 (70%) | |
| **ICI discontinuation due to IRAE, No. (%)** | 247 | | | | **0.018** | 210 | | | | **0.014** |
| Yes | | 25 (18%) | 32 (30%) | 57 (23%) | | | 17 (16%) | 32 (30%) | 49 (23%) | |
| No | | 117 (82%) | 73 (70%) | 190 (77%) | | | 88 (84%) | 73 (70%) | 161 (77%) | |
| **Grade 3-5 IRAE, No. (%)*** | 247 | | | | **0.004** | 210 | | | | **0.004** |
| Yes | | 29 (20%) | 39 (37%) | 68 (28%) | | | 20 (19%) | 39 (37%) | 59 (28%) | |
| No | | 113 (80%) | 66 (63%) | 179 (72%) | | | 85 (81%) | 66 (63%) | 151 (72%) | |

* Denominator: Cases with positive IRAE (annotated as IRAE = Yes in the table)
† One of the 5 PSM models run after multiple imputations; the numbers varied very slightly among the 5 runs.
+ Three patients had both hypothyroidism and adrenal insufficiency.
# One patient had both hypothyroidism and adrenal insufficiency.
& Two patients had both hypothyroidism and adrenal insufficiency.
^ One patient had both hypothyroidism and adrenal insufficiency.

Table 3. Seasonal distribution of IRAE occurrence

| | | Before Propensity Score Matching | | | | After Propensity Score Matching† | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **N** | **FV-Positive** (N=67) | **FV-Negative** (N=55) | **Combined** (N=122) | **P-value** | **N** | **FV-Positive** (N=50) | **FV-Negative** (N=55) | **Combined** (N=105) | **P-value** |
| **Season of IRAE, No. (%)** | 122 | | | | 0.620 | 105 | | | | 0.464 |
| Spring | | 15 (22%) | 9 (16%) | 24 (20%) | | | 12 (24%) | 9 (16%) | 21 (20%) | |
| Summer | | 17 (25%) | 16 (29%) | 33 (27%) | | | 15 (30%) | 16 (29%) | 31 (30%) | |
| Fall | | 12 (18%) | 14 (25%) | 26 (21%) | | | 7 (14%) | 14 (25%) | 21 (20%) | |
| Winter | | 23 (35%) | 16 (30%) | 39 (32%) | | | 16 (32%) | 16 (30%) | 32 (30%) | |
| **Flu season of IRAE, No. (%)** | 122 | | | | 0.799 | 105 | | | | 0.382 |
| Fall/Winter | | 35 (52%) | 30 (55%) | 65 (53%) | | | 23 (46%) | 30 (55%) | 53 (50%) | |
| Spring/Summer | | 32 (48%) | 25 (45%) | 57 (47%) | | | 27 (54%) | 25 (45%) | 52 (50%) | |

**Table 4.** Associations between clinical features and immune-related adverse events using ordinal logistic regression analysis

| | **Grade 3-5 IRAE vs Grade 1-2 IRAE vs No IRAE** | | |
|---|---|---|---|
| | **OR** | **90% CI** | **P-value** |
| **FV** - Positive vs. Negative (ref) | **0.63** | (0.40 to 0.99) | **0.046** |
| **Race** - White vs. Non-White (ref) | **3.27** | (1.13 to 9.47) | **0.034** |
| **Gender** - Male vs. Female (ref) | 0.93 | (0.57 to 1.53) | 0.406 |
| **Smoking Status** - Ever vs. Never (ref) | 2.86 | (0.97 to 8.42) | 0.055 |
| **Age** - < 60 vs. ≥ 60 (ref) | 0.86 | (0.49 to 1.52) | 0.335 |
| **Trial** - Yes vs. No (ref) | 1.23 | (0.73 to 2.07) | 0.254 |
| **ICI received** - | | | |
| PD-L1 vs. PD-1 (ref) | 2.36 | (0.94 to 5.90) | 0.062 |
| CTLA-4/CTLA-4 combinations vs. PD-1 (ref) | 2.06 | (0.97 to 4.38) | 0.057 |

Harrell's c-statistics = 0.642

**Table 5.** Associations between clinical features and severe immune-related adverse events using logistic regression analysis

| | **Grade 3-5 IRAE vs Grade 1-2 IRAE plus No IRAE*** | | |
|---|---|---|---|
| | **OR** | **90% CI** | **P-value** |
| **FV** - Positive vs. Negative (ref)[†] | **0.42** | (0.24 to 0.73) | **0.005** |
| **Race** - White vs. Non-White (ref) | 1.94 | (0.60 to 6.25) | 0.175 |
| **Gender** - Male vs. Female (ref) | 0.90 | (0.51 to 1.58) | 0.378 |
| **Smoking Status** - Ever vs. Never (ref) | 4.34 | (0.73 to 25.76) | 0.088 |
| **Age** - < 60 vs. ≥ 60 (ref) | 0.99 | (0.53 to 1.85) | 0.489 |
| **Trial** - Yes vs. No (ref) | 0.78 | (0.41 to 1.46) | 0.257 |
| **ICI received** - | | | |
| PD-L1 vs. PD-1 (ref) | 2.24 | (0.87 to 5.79) | 0.081 |
| CTLA-4/CTLA-4 combinations vs. PD-1 (ref) | **2.89** | (1.22 to 6.87) | **0.022** |

*Comparisons made between patients with **Grade 3-5** IRAE and patients with no IRAE plus patients with **Grade 1-2** IRAE.
Harrell's c-statistics = 0.695.
[†] OR=0.45 by Elastic-net logistic regression with $\alpha$=0.5; OR=0.61 by Bayesian logistic regression with horseshoe prior

**Table 6.** Subset analysis for the associations between clinical features and IRAE

| | Grade 3-5 IRAE vs No IRAE | | |
|---|---|---|---|
| | **OR** | **90% CI** | **P-value** |
| **FV** - Positive vs. Negative (ref) | **0.46** | (0.26 to 0.84) | **0.016** |
| **Race** - White vs. Non-White (ref) | 2.70 | (0.79 to 9.25) | 0.092 |
| **Gender** - Male vs. Female (ref) | 0.89 | (0.48 to 1.67) | 0.382 |
| **Smoking Status** - Ever vs. Never (ref) | 4.97 | (0.82 to 30.18) | 0.072 |
| **Age** - < 60 vs. ≥ 60 (ref) | 0.86 | (0.43 to 1.72) | 0.357 |
| **Trial** - Yes vs. No (ref) | 0.94 | (0.48 to 1.85) | 0.439 |
| **ICI received** | | | |
| PD-L1 vs. PD-1 (ref) | 2.80 | (0.91 to 8.61) | 0.065 |
| CTLA-4/CTLA-4 combinations vs. PD-1 (ref) | **2.95** | (1.13 to 7.72) | **0.032** |

Harrell's c-statistics = 0.691

**Table 7.** Associations between clinical features and survival (PFS and OS)

| | PFS | | | OS | | |
|---|---|---|---|---|---|---|
| | **HR** | **90% CI** | **P-value** | **HR** | **90% CI** | **P-value** |
| **FV** - Positive vs. Negative (ref) | 0.96 | (0.73 to 1.26) | 0.395 | 1.06 | (0.79 to 1.43) | 0.371 |
| **Race** - White vs. Non-White (ref) | 0.70 | (0.45 to 1.11) | 0.100 | 1.03 | (0.59 to 1.80) | 0.465 |
| **Gender** - Male vs. Female (ref) | 0.81 | (0.62 to 1.05) | 0.091 | 0.97 | (0.72 to 1.30) | 0.427 |
| **Smoking Status** - Ever vs. Never (ref) | 0.80 | (0.48 to 1.33) | 0.235 | 1.14 | (0.61 to 2.15) | 0.363 |
| **Age** - < 60 vs. ≥ 60 (ref) | 1.19 | (0.88 to 1.60) | 0.176 | 0.96 | (0.68 to 1.37) | 0.428 |
| **Trial** - Yes vs. No (ref) | **0.71** | (0.53 to 0.95) | **0.026** | **0.60** | (0.43 to 0.83) | **0.005** |
| **ICI received** | | | | | | |
| PD-L1 vs. PD-1 (ref) | 0.60 | (0.34 to 1.07) | 0.074 | 0.56 | (0.28 to 1.12) | 0.083 |
| CTLA-4/CTLA-4 combinations vs. PD-1 (ref) | 1.17 | (0.77 to 1.78) | 0.264 | 1.26 | (0.80 to 1.99) | 0.202 |

Harrell's c-statistics for PFS = 0.541 and for OS = 0.542

**Supplemental Material**

# Associations of Influenza Vaccination with Severity of Immune-Related Adverse Events in Patients with Advanced Thoracic Cancers on Immune Checkpoint Inhibitors

## Appendix

I. **Types of Comorbidity**

II. **Precision Analysis (eTable 1-2)**

III. **Sensitivity Analysis I (eTable 3-6; eFigure 1)**

IV. **Sensitivity Analysis II (eTable 7-10; eFigure 2)**

V. **Survival curves (eFigure 3)**

## Types of Comorbidity

Cardiovascular comorbidities were defined as any of the following: coronary artery disease, congestive heart failure, atrial fibrillation, cardiac arrhythmias not otherwise specified [NOS], conduction block, aortic aneurysm, valvular heart disease, pulmonary embolism, and peripheral vascular disease. Pulmonary comorbidities were defined as any of the following: COPD, asthma, pulmonary fibrosis, obstructive sleep apnea. Metabolic comorbidities were defined as any of the following: diabetes mellitus, dyslipidemia, metabolic syndrome, steatocystoma multiplex, and osteoporosis. Autoimmune comorbidities were defined as any of the following: rheumatoid arthritis, lupus, Sjogren syndrome, Crohn's disease, ulcerative colitis, autoimmue thyroiditis, and antiphospholipid syndrome. Renal comorbidities were defined as any of the following: chronic kidney disease, renal artery stenosis, and renal stones. Cerebrovascular comorbidities were defined as any of the following: stroke, brain aneurysm, and transient ischemic attack. Neurological comorbidities were defined as any of the following: Parkinson's disease, multiple sclerosis, torticollis, meningitis NOS, migraine and dementia. Neuromuscular IRAE were defined as any of the following: encephalitis NOS, acute encephalopathy, peripheral neuropathy, Bell's palsy, restless leg syndrome, myalgia, progression of multiple sclerosis, and polymyositis.

## Precision Analysis

The precision analysis was performed using simulation studies with 5,000 runs to estimate the odds ratio (OR) and half-width of 90% confidence interval (CI) based on univariate ordinal logistic regression model with outcome IRAE (grade 3-5, grade 1-2, No) and exposure variable FV-Positive vs. FV-Negative. Simulation dataset was generated using parameters on the left hand side of the table, taking eTable 1 as an example, 142 FV-Positive samples were generated with 29% grade 3-5 IRAE, 38% grade 1-2 IRAE and 75% no IRAE; and 105 FV-Negative samples were generated with 39% grade 3-5 IRAE, 16% grade 1-2 IRAE and 50% no IRAE. Then, the ordinal logistic regression model was used to estimate OR of FV-Positive vs. FV-Negative. Replicating the above process for 5,000 times, we obtained 5,000 ORs, the average of the ORs and the 95% confidence interval consisting of 0.025 and 0.975 percentiles of the ORs. The half-width of the 95% confidence interval of the estimated odds ratio is less than 0.28.

**eTable 1.** Original dataset – summary statistics of IRAE stratified by FV-Positive vs. FV-Negative; estimated OR with its 90% CI as well as the half-width of 90% CI of the estimated OR.

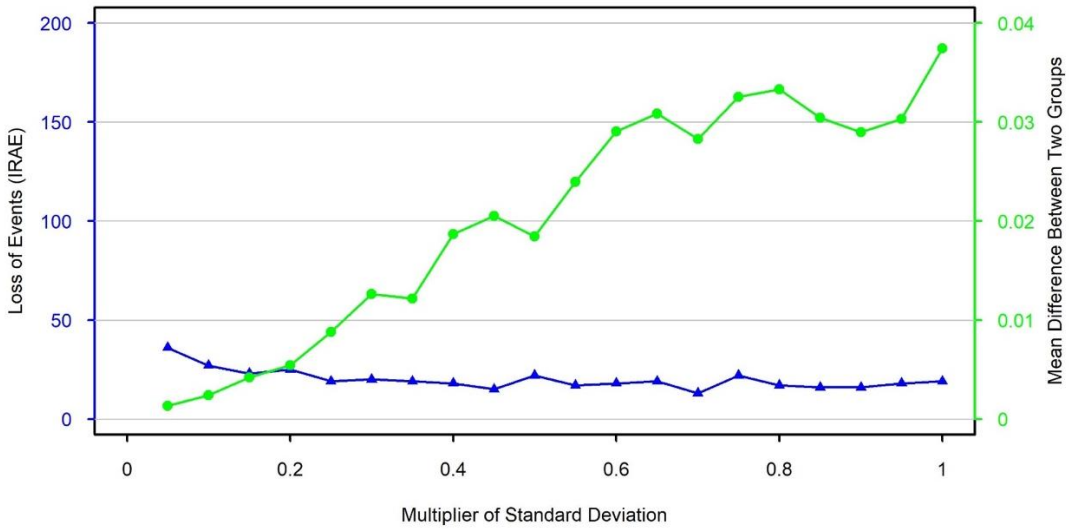
| | FV-Positive (N=142) | FV-Negative (N=105) | Combined (N=247) | Estimated OR (90% CI) | Half-width of 95% CI of the estimated OR |
|---|---|---|---|---|---|
| Grade 3-5 IRAE | 29 (20%) | 39 (37%) | 68 (28%) | 0.67 (0.43 to 0.98) | 0.28 |
| Grade 1-2 IRAE | 38 (27%) | 16 (15%) | 54 (22%) | | |
| No IRAE | 75 (53%) | 50 (48%) | 125 (50%) | | |

**eTable 2.** Imputation data set 1 (after PSM) – summary statistics of IRAE stratified by FV-Positive vs. FV-Negative; estimated OR with its 90% CI as well as the half-width of 90% CI of the estimated OR.

| | FV-Positive (N=105) | FV-Negative (N=105) | Combined (N=210) | Estimated OR (95% CI) | Half-width of 95% CI of the estimated OR |
|---|---|---|---|---|---|
| Grade 3-5 IRAE | 20 (19%) | 39 (37%) | 59 (28%) | 0.66 (0.42 to 0.96) | 0.27 |
| Grade 1-2 IRAE | 30 (29%) | 16 (15%) | 46 (22%) | | |
| No IRAE | 55 (52%) | 50 (48%) | 105 (50%) | | |

## Sensitivity Analysis I

Propensity-score nearest neighbor matching without replacement was performed based on logistic regression model, generating 1:1 matched cohort of FV-negative to FV-positive with caliper 0.2 of standard deviation of propensity score. The caliper was selected according to eFigure 1. The optimal value of 0.2 was selected to have mean difference of propensity score between FV-positive and FV-negative groups as small as possible as well as number of loss of events. The following potential confounders were included in PSM model: race (white vs non-white), gender (male vs female), age (<60 vs ≥60 years), smoking status (ever smoker vs never smoker), trial patients (yes vs no), ICI received (PD-L1, PD1 vs CTLA-4/CTLA-4 combinations), cardiovascular (yes vs no), pulmonary (yes vs no), second primary cancers (yes vs no), metabolic (yes vs no), autoimmune (yes vs no), other comorbidities (yes vs no; other comorbidities defined as renal, cerebrovascular or neurological comorbidities).




**eFigure 1**. Number of loss of events and mean difference of propensity score between FV-positive and FV-negative groups at each multiplier of standard deviation.

**eTable 3.** Sensitivity analysis I - Associations between clinical features and immune-related adverse events using ordinal logistic regression analysis

| | Grade 3-5 IRAE vs Grade 1-2 IRAE vs No IRAE | | |
|---|---|---|---|
| | **OR** | **90% CI** | **P-value** |
| **FV** - Positive vs. Negative (ref) | 0.65 | (0.39 to 1.07) | 0.077 |
| **Race** - White vs. Non-White (ref) | 2.86 | (0.97 to 8.38) | 0.054 |
| **Gender** - Male vs. Female (ref) | 0.93 | (0.58 to 1.49) | 0.393 |
| **Smoking Status** - Ever vs. Never (ref) | 3.63 | (0.97 to 13.65) | 0.054 |
| **Age** - < 60 vs. ≥ 60 (ref) | 0.90 | (0.53 to 1.53) | 0.369 |
| **Trial** - Yes vs. No (ref) | 1.14 | (0.65 to 2.01) | 0.350 |
| **ICI received** - | | | |
| PD-L1 vs. PD-1 (ref) | 2.13 | (0.95 to 4.77) | 0.062 |
| CTLA-4/CTLA-4 combinations vs. PD-1 (ref) | 2.13 | (0.95 to 4.77) | 0.061 |

Harrell's c-statistics = 0.638

**eTable 4.** Sensitivity analysis I - Associations between clinical features and severe immune-related adverse events using logistic regression analysis

| | Grade 3-5 IRAE vs Grade 1-2 IRAE plus No IRAE | | |
|---|---|---|---|
| | **OR** | **90% CI** | **P-value** |
| **FV** - Positive vs. Negative (ref) † | 0.44 | (0.23 to 0.83) | 0.017 |
| **Race** - White vs. Non-White (ref) | 1.84 | (0.54 to 6.26) | 0.205 |
| **Gender** - Male vs. Female (ref) | 0.86 | (0.48 to 1.51) | 0.327 |
| **Smoking Status** - Ever vs. Never (ref) | 5.24 | (0.89 to 30.95) | 0.063 |
| **Age** - < 60 vs. ≥ 60 (ref) | 1.04 | (0.56 to 1.94) | 0.458 |
| **Trial** - Yes vs. No (ref) | 0.78 | (0.37 to 1.62) | 0.286 |
| **ICI received** - | | | |
| PD-L1 vs. PD-1 (ref) | 2.23 | (0.93 to 5.36) | 0.066 |
| CTLA-4/CTLA-4 combinations vs. PD-1 (ref) | 3.19 | (1.30 to 7.86) | 0.017 |

*Comparisons made between patients with grade 3-5 IRAE and patients with no IRAE plus patients with grade 1-2 IRAE.

Harrell's c-statistics = 0.693

† OR=0.45 by Elastic-net logistic regression with $\alpha$=0.5; OR=0.70 by Bayesian logistic regression with horseshoe prior

**eTable 5.** Sensitivity analysis I - Subset analysis for the associations between clinical features and IRAE

| | Grade 3-5 IRAE vs No IRAE | | |
|---|---|---|---|
| | **OR** | **90% CI** | **P-value** |
| **FV** - Positive vs. Negative (ref) | 0.48 | (0.25 to 0.92) | 0.032 |
| **Race** - White vs. Non-White (ref) | 2.50 | (0.72 to 8.61) | 0.112 |
| **Gender** - Male vs. Female (ref) | 0.85 | (0.45 to 1.57) | 0.328 |
| **Smoking Status** - Ever vs. Never (ref) | 6.09 | (0.98 to 37.66) | 0.052 |
| **Age** - < 60 vs. ≥ 60 (ref) | 0.89 | (0.45 to 1.74) | 0.387 |
| **Trial** - Yes vs. No (ref) | 0.91 | (0.42 to 1.97) | 0.418 |
| **ICI received** | | | |
| PD-L1 vs. PD-1 (ref) | 2.59 | (0.98 to 6.84) | 0.054 |
| CTLA-4/CTLA-4 combinations vs. PD-1 (ref) | 3.12 | (1.15 to 8.44) | 0.030 |

Harrell's c-statistics = 0.691

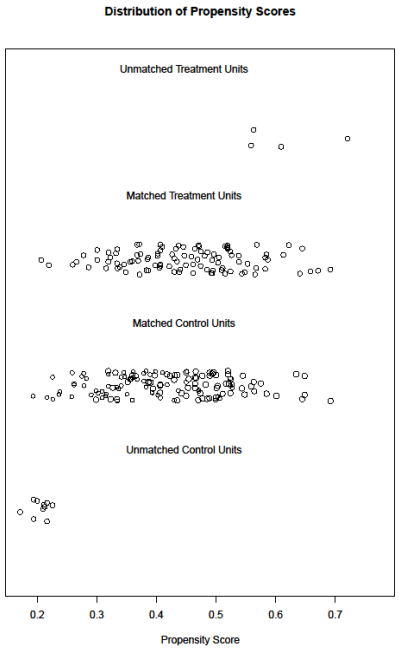
**eTable 6.** Sensitivity analysis I - Associations between clinical features and survival (PFS and OS)

| | PFS | | | OS | | |
|---|---|---|---|---|---|---|
| | **HR** | **90% CI** | **P-value** | **HR** | **90% CI** | **P-value** |
| **FV** - Positive vs. Negative (ref) | 0.94 | (0.72 to 1.24) | 0.359 | 1.11 | (0.81 to 1.54) | 0.290 |
| **Race** - White vs. Non-White (ref) | 0.71 | (0.41 to 1.24) | 0.155 | 1.03 | (0.54 to 1.97) | 0.467 |
| **Gender** - Male vs. Female (ref) | 0.81 | (0.60 to 1.08) | 0.115 | 1.00 | (0.73 to 1.38) | 0.499 |
| **Smoking Status** - Ever vs. Never (ref) | 0.77 | (0.44 to 1.35) | 0.225 | 1.07 | (0.56 to 2.04) | 0.432 |
| **Age** - < 60 vs. ≥ 60 (ref) | 1.13 | (0.84 to 1.53) | 0.247 | 0.97 | (0.67 to 1.40) | 0.449 |
| **Trial** - Yes vs. No (ref) | 0.74 | (0.52 to 1.04) | 0.071 | 0.66 | (0.44 to 0.97) | 0.039 |
| **ICI received** | | | | | | |
| PD-L1 vs. PD-1 (ref) | 0.65 | (0.37 to 1.13) | 0.099 | 0.63 | (0.34 to 1.18) | 0.114 |
| CTLA-4/CTLA-4 combinations vs. PD-1 (ref) | 1.13 | (0.71 to 1.81) | 0.328 | 1.14 | (0.67 to 1.95) | 0.344 |

Harrell's c-statistics for PFS = 0.533 and for OS = 0.523

## Sensitivity Analysis II

Propensity-score nearest neighbor matching without replacement was performed based on logistic regression model, generating 1:2 matched cohort of FV-negative to FV-positive with caliper 0.25 of standard deviation of propensity score. The caliper was selected according to eFigure 2. The optimal value of 0.25 was selected to keep as many cases as possible in the study cohort. The following potential confounders were included in PSM model: race (white vs non-white), gender (male vs female), age (<60 vs ≥60 years), smoking status (ever smoker vs never smoker), trial patients (yes vs no), ICI received (PD-L1, PD1 vs CTLA-4/CTLA-4 combinations), cardiovascular (yes vs no), pulmonary (yes vs no), second primary cancers (yes vs no), metabolic (yes vs no), autoimmune (yes vs no), other comorbidities (yes vs no; other comorbidities defined as renal, cerebrovascular or neurological comorbidities).




**eFigure 2.** Distribution of propensity score

**eTable 7.** Sensitivity analysis II - Associations between clinical features and immune-related adverse events using ordinal logistic regression analysis

| | Grade 3-5 IRAE vs Grade 1-2 IRAE vs No IRAE | | |
|---|---|---|---|
| | **OR** | **90% CI** | **P-value** |
| **FV** - Positive vs. Negative (ref) | 0.67 | (0.43 to 1.03) | 0.064 |
| **Race** - White vs. Non-White (ref) | 2.32 | (0.98 to 5.49) | 0.054 |
| **Gender** - Male vs. Female (ref) | 0.81 | (0.52 to 1.26) | 0.216 |
| **Smoking Status** - Ever vs. Never (ref) | 3.60 | (1.24 to 10.41) | 0.024 |
| **Age** - < 60 vs. ≥ 60 (ref) | 0.81 | (0.50 to 1.30) | 0.232 |
| **Trial** - Yes vs. No (ref) | 1.13 | (0.70 to 1.83) | 0.333 |
| **ICI received** - | | | |
| PD-L1 vs. PD-1 (ref) | 2.05 | (1.02 to 4.15) | 0.046 |
| CTLA-4/CTLA-4 combinations vs. PD-1 (ref) | 2.35 | (1.09 to 5.05) | 0.033 |

Harrell's c-statistics = 0.635

**eTable 8.** Sensitivity analysis II - Associations between clinical features and severe immune-related adverse events using logistic regression analysis

| | Grade 3-5 IRAE vs Grade 1-2 IRAE plus No IRAE | | |
|---|---|---|---|
| | **OR** | **90% CI** | **P-value** |
| **FV** - Positive vs. Negative (ref) † | 0.45 | (0.27 to 0.75) | 0.005 |
| **Race** - White vs. Non-White (ref) | 1.61 | (0.60 to 4.36) | 0.215 |
| **Gender** - Male vs. Female (ref) | 0.79 | (0.46 to 1.35) | 0.231 |
| **Smoking Status** - Ever vs. Never (ref) | 4.84 | (0.74 to 31.75) | 0.084 |
| **Age** - < 60 vs. ≥ 60 (ref) | 0.93 | (0.52 to 1.65) | 0.414 |
| **Trial** - Yes vs. No (ref) | 0.69 | (0.37 to 1.29) | 0.164 |
| **ICI received** - | | | |
| PD-L1 vs. PD-1 (ref) | 2.18 | (1.00 to 4.74) | 0.050 |
| CTLA-4/CTLA-4 combinations vs. PD-1 (ref) | 3.74 | (1.61 to 8.68) | 0.005 |

*Comparisons made between patients with grade 3-5 IRAE and patients with no IRAE plus patients with grade 1-2 IRAE.

Harrell's c-statistics = 0.698

† OR=0.45 by Elastic-net logistic regression with $\alpha$=0.5; OR=0.65 by Bayesian logistic regression with horseshoe prior

**eTable 9.** Sensitivity analysis II - Subset analysis for the associations between clinical features and IRAE

| | Grade 3-5 IRAE vs No IRAE | | |
|---|---|---|---|
| | **OR** | **90% CI** | **P-value** |
| **FV** - Positive vs. Negative (ref) | 0.50 | (0.29 to 0.88) | 0.022 |
| **Race** - White vs. Non-White (ref) | 2.10 | (0.76 to 5.83) | 0.116 |
| **Gender** - Male vs. Female (ref) | 0.73 | (0.41 to 1.3) | 0.184 |
| **Smoking Status** - Ever vs. Never (ref) | 6.02 | (0.93 to 38.97) | 0.057 |
| **Age** - < 60 vs. ≥ 60 (ref) | 0.78 | (0.42 to 1.45) | 0.257 |
| **Trial** - Yes vs. No (ref) | 0.86 | (0.43 to 1.71) | 0.360 |
| **ICI received** | | | |
| PD-L1 vs. PD-1 (ref) | 2.50 | (1.07 to 5.85) | 0.038 |
| CTLA-4/CTLA-4 combinations vs. PD-1 (ref) | 3.52 | (1.35 to 9.15) | 0.015 |

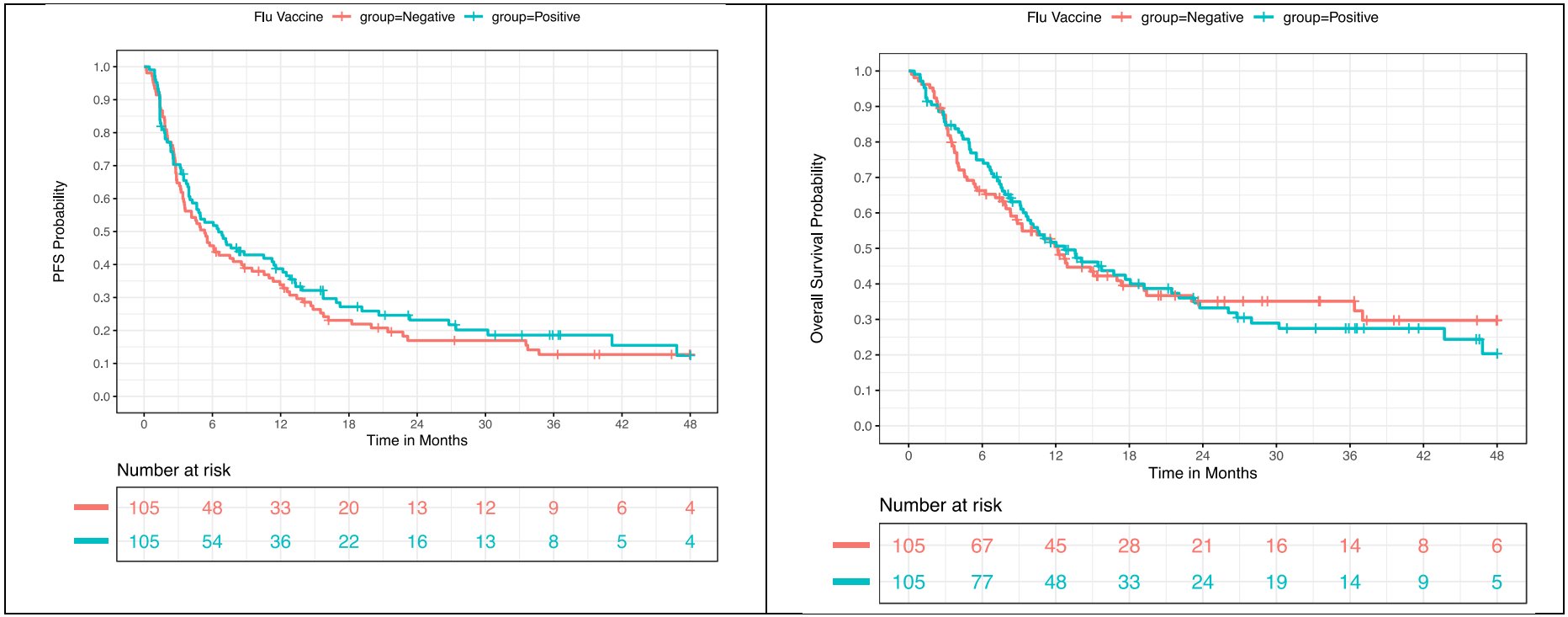
Harrell's c-statistics = 0.690

**eTable 10.** Sensitivity analysis II - Associations between clinical features and survival (PFS and OS)

| | PFS | | | OS | | |
|---|---|---|---|---|---|---|
| | **HR** | **90% CI** | **P-value** | **HR** | **90% CI** | **P-value** |
| **FV** - Positive vs. Negative (ref) | 0.90 | (0.70 to 1.16) | 0.254 | 1.04 | (0.79 to 1.38) | 0.404 |
| **Race** - White vs. Non-White (ref) | 0.78 | (0.51 to 1.19) | 0.165 | 1.09 | (0.66 to 1.82) | 0.387 |
| **Gender** - Male vs. Female (ref) | 0.80 | (0.62 to 1.03) | 0.077 | 0.95 | (0.71 to 1.26) | 0.383 |
| **Smoking Status** - Ever vs. Never (ref) | 0.70 | (0.43 to 1.14) | 0.114 | 1.01 | (0.57 to 1.81) | 0.487 |
| **Age** - < 60 vs. ≥ 60 (ref) | 1.15 | (0.88 to 1.52) | 0.195 | 0.99 | (0.72 to 1.35) | 0.477 |
| **Trial** - Yes vs. No (ref) | 0.71 | (0.54 to 0.93) | 0.020 | 0.59 | (0.43 to 0.80) | 0.003 |
| **ICI received** | | | | | | |
| PD-L1 vs. PD-1 (ref) | 0.70 | (0.44 to 1.13) | 0.110 | 0.71 | (0.41 to 1.21) | 0.145 |
| CTLA-4/CTLA-4 combinations vs. PD-1 (ref) | 1.22 | (0.80 to 1.87) | 0.214 | 1.32 | (0.84 to 2.09) | 0.159 |

Harrell's c-statistics for PFS = 0.547 and for OS = 0.537

# Survival curves




**eFigure 3.** (A) KM plot of PFS in thoracic cancer patients. (B) KM plot of OS in thoracic cancer patients.