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Original Article

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Prognostic Implications of Timing of Immunotherapy in Stage IV Non-Small Cell Lung Cancer

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Abstract

Background: Currently, the established approach for addressing stage IV non-small cell lung cancer (NSCLC) involves combining chemotherapy with immunotherapy. However, the necessity for molecular analysis prior to commencing immunotherapy often results in a delay in its initiation following the commencement of chemotherapy. Therefore, this study aimed to study the significance of postponing immunotherapy on pertinent patient outcomes.

Methods: Using the National Cancer Database (NCBD), patients diagnosed with stage IV NSCLC between 2017 and 2018 were screened. Inclusion criteria comprised those treated with multi-agent chemotherapy as the first-line therapy within 30 days of treatment, surviving beyond 2 months of diagnosis, and absence of neuroendocrine pathology. Patients were grouped among those receiving immunotherapy within 30 days of chemotherapy, immunotherapy within 31 - 60 days of chemotherapy, or chemotherapy alone. Clinical characteristics were collected and their correlation with the timing of immunotherapy was evaluated. The impact of delaying immunotherapy on overall survival (OS) was investigated using Kaplan-Meier analysis. Multivariate Cox regression analysis was employed to identify independent prognostic variables associated with OS.

Results: Our cohort comprised 99,008 patients with clinical stage IV NSCLC diagnosed between 2017 and 2018, which were distributed in the three treatment groups described above. Patients receiving immunotherapy within 30 days of chemotherapy showed greater OS in contrast to both those subjected to delayed immunotherapy (hazard ratio (HR) = 0.74, 95% confidence interval (CI): 0.64 - 0.87, P = 0.0003). Subsequent multivariate regression analysis showed that postponing immunotherapy, older age, male sex, white race, non-adenocarcinoma histology, higher clinical N stage, use of radiation treatment, and presence of liver metastasis were all associated with worse OS.

Conclusions: Introducing immunotherapy within the first 30 days of chemotherapy initiation significantly increases survival in patients with stage IV NSCLC.

Keywords: Non-small cell lung cancer; Immunotherapy; Combination therapy

Introduction

Lung cancer remains a burden for global medicine given its high prevalence and lethality worldwide, being the leading cause of cancer mortality in males and the second in females; in addition, it is more common in men than females [1]. In the USA, there has been a steady decline of lung cancer incidence and mortality in the last decades, especially in the male population, mainly due to advances in therapy and screening strategies [2].

Once diagnosed, lung cancer classification depends on a combination of morphological, immunohistochemical and molecular analysis of the tumor according to the World Health Organization (WHO) classification [3]. Once analyzed, lung cancer is divided into two major groups, small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), with the latter including other subgroups such as adenocarcinoma, squamous cell, and large cell carcinoma [4].

Excluding oncogene-driven disease, a combination of cytotoxic chemotherapy and immune checkpoint inhibitor (i.e., anti- programmed cell death 1 (PD1)/programmed cell death ligand 1 (PDL1) inhibitors) became a standard management in stage IV NSCLC in 2017 according to the National Comprehensive Cancer Network (NCCN) guidelines (version 2.2024). Cases with a positive driver oncogene such as *EGFR* NSCLC, however, need to be treated with rather appropriate targeted therapy. In routine practice, a lengthy turnaround time of molecular analysis to rule out oncogenes makes the chemoimmunotherapy combination a challenge.

In addition, unexpected toxicities when immunotherapy

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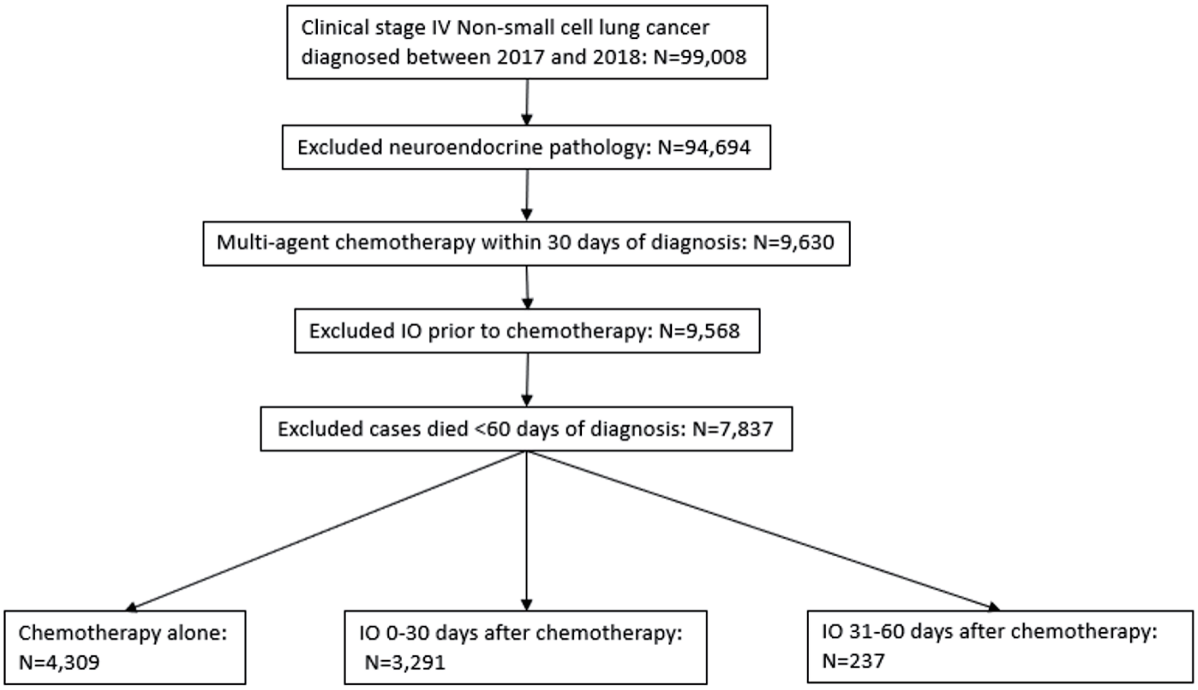

Figure 1. Selection criteria according to CONSORT diagram. Deidentified cases were released from the National Cancer Database. IO: immunotherapy.

and targeted therapy are combined or sequenced have been reported [5-7]. Because of these restrictions many oncologists often initiate traditional chemotherapy alone for the first few cycles until a molecular result becomes available so that they can modify the first-line therapy accordingly. This practice pattern to delay initiation of immunotherapy may lead to inferior cancer outcome.

Keynote-189, an international phase III trial defining the role of additive pembrolizumab to first-line chemotherapy, demonstrated an advantage in overall survival (OS) of chemo-immunotherapy combination over chemotherapy alone regardless of PDL1 status. In the arm of chemotherapy alone, approximately 40% of patients received immunotherapy as second-line therapy. Despite the cross-over of the arms, this study showed a statistically significant difference in OS, suggesting the importance of early exposure to immunotherapy. Impact of delayed administration of immunotherapy in first-line therapy is unknown, which constitutes the main purpose of this study.

Materials and Methods

The National Cancer Database (NCDB) is a joint project of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society. The CoC's NCDB and the hospitals participating in the CoC NCDB are the sources of the deidentified data used herein; however, they have not verified the statistical validity of the data analysis, or the conclusions derived by the authors, and they are not responsible for them. The data are considered hospital-based rather than population-based [8]. Of note, this study was reviewed by the Institutional Review Board at Penn State Health and was designated exempt from human subject research.

Patients with stage IV NSCLC who were diagnosed between 2017 and 2018 were screened (n = 99,008). Those treated with multi-agent chemotherapy as a first course of therapy were included. Those with neuroendocrine pathology were excluded. In addition, patients treated with multi-agent chemotherapy within 30 days of diagnosis were included; those who were exposed to immunotherapy prior to chemotherapy were also excluded. Patients who survived less than 60 days of diagnosis were excluded as well (Fig. 1).

After applying initial inclusion and exclusion criteria, eligible patients were then assigned to a group of: 1) those who received early immunotherapy within 30 days of chemotherapy; 2) delayed immunotherapy within 31 - 60 days of chemotherapy; or 3) chemotherapy alone.

The main outcome variable of this study is OS, which is defined as the length of time from the initial diagnosis to death of any causes or last follow-up. Key clinical characteristics were obtained and examined within each group. These included age (< 70 versus 70 or more), sex (male versus female), race (White versus others), institution (academic versus others), Charlson-Deyo comorbidity score, year of diagnosis (2017 versus 2018), cell type (adenocarcinoma not otherwise specified versus others), clinical T stage (cT3-4 versus other), clinical N stage (cN2-N3 versus others), clinical M stage (cM1BC versus other), surgery (yes versus no), radiation (yes versus no), presence of brain and liver metastasis (yes versus no). A propensity score matching (PSM) analysis was conducted to compare groups 1) and 2).

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Statistical methods

The associations between clinical demographics and timing of immunotherapy were examined using Chi-square tests. Kaplan-Meier survival curves were generated and compared between timing of immunotherapy groups using log-rank test. Univariable and multivariable Cox proportional hazard regression models were used to calculate hazard ratios (HRs) and their 95% confidence intervals (CIs) for survival since time of tissue diagnosis, and independent prognostic factors were identified. In the analysis of patients with stage IV NSCLC who received immunotherapy within 0 - 30 days and 31 - 60 of chemotherapy, PSM was performed to reduce bias in our selected sample. The following variables were used in PSM: age, sex, race, surgery, radiation, liver metastasis, clinical M stage, clinical N stage, and histology. PSM was performed using "MatchIt" package version 4.5.5 running on R version 4.4.0 (R Foundation for Statistical Computing, Vienna, Austria). One-to-one nearest neighbor matching was done with propensity scores estimated through logistic regression. All other analyses were performed using JMP® 14.0 (SAS Institute Inc., Cary, NC, USA). All tests are two-sided, and $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

Our sample selection process is described in Figure 1. The study included 99,008 patients diagnosed with clinical stage IV NSCLC between 2017 and 2018. After applying exclusion criteria, 7,837 patients were assigned for group distribution (Fig. 1). Among these, 3,291 received immunotherapy (0 - 30 days from diagnosis), 237 received delayed immunotherapy (31 - 60 days from diagnosis), and 4,309 received chemotherapy only. Patients' characteristics and the associations between immunotherapy use and clinical factors are presented in Table 1. Characteristics associated with immunotherapy use were male sex, age less than 70, White race, histology of adenocarcinoma, clinical T stage (other than T3-4), clinical M stage (cM1BC), and no radiation therapy.

We successfully matched 237 patients in group 1 with the patients in group 2 using propensity score. The characteristics after PSM were shown here (Supplementary Material 1, www.wjon.org). No significant differences in patient characteristics were found between the matched patients in groups 1 and 2.

Early immunotherapy within 30 days of initiation of chemotherapy prolongs OS among NSCLC patients

A total of 3291,237, and 4,309 were selected for groups 1, 2, 3 for the analysis, respectively. Among these groups, median OS was 14.5, 9.5, and 10.0 months for the group 1, 2, and 3, respectively. A statistically significant difference in OS was observed between groups 1 and 2 (HR = 0.74, 95% CI: 0.64 - 0.87, P = 0.0003) (Table 2, Fig. 2). There was no statistically significant difference in OS between groups 2 and 3. The significant OS difference between groups 1 and 2 was confirmed by PSM analysis (n = 237 each, HR = 0.73, 95% CI: 0.59 - 0.90, P = 0.004) (Fig. 3).

Furthermore, multivariate Cox regression analysis demonstrated that group 1 had a significantly prolonged OS over group 2, and that immunotherapy use in relation to chemotherapy was an independent predictor of increased OS whereas delayed immunotherapy was associated with decreased OS (Table 2). This relation persisted after PSM analysis (Supplementary Material 2, www.wjon.org). In addition, age higher than 70, male sex, White race, non-adenocarcinoma histology, N2-3 stage, use of radiotherapy and presence of liver metastasis were all independent predictors of poor OS in this group of patients (Table 2). After PSM analysis, only male sex, non-adenocarcinoma histology and the presence of liver metastasis remained as independent predictors (Supplementary Material 2, www.wjon.org).

Discussion

To our knowledge, this is the first study evaluating the prognostic implications of the timing of immunotherapy in combination with chemotherapy in patients with stage IV NSCLC. We demonstrated that early introduction of immunotherapy within 30 days of starting chemotherapy was associated with a significantly increased OS, which was further validated on multivariate and PSM analyses. This finding could be the result of chemotherapy-mediated enhancement of the immune response to cancerous cells, by modifying their structure so they are more detectable to the immune system, while simultaneously decreasing cancer-mediated immunomodulation [9]. The addition of immunotherapy to further potentiate this response would translate to better clinical outcomes.

To further support this, several clinical trials have demonstrated significant improvement in several outcomes, including survival for patients with NSCLC when combining immunotherapy and chemotherapy. One of the most relevant trials in this regard is, as mentioned previously, the KEYNOTE-189 study, which investigated the efficacy of pembrolizumab in combination with standard chemotherapy for patients with metastatic non-squamous NSCLC, successfully demonstrating substantial increase in OS and progression-free survival (PFS) in patients with combination therapy. Moreover, this combination did not increase the frequency of adverse events attributed to chemotherapy or immunotherapy alone [10]. Another notable trial is the CheckMate-227 study, which randomized patients with stage IV or recurrent NSCLC to receive either a combination of nivolumab plus ipilimumab, nivolumab with chemotherapy or chemotherapy alone in patients. The results showed greater OS, treatment response, and PFS with the combination immunotherapy and immunotherapy plus chemotherapy regimens compared to chemotherapy alone [11]. Furthermore, there are ongoing trials evaluating whether combining immunotherapy and chemotherapy as front-line therapy after diagnosis is superior to using both treatment strategies separately, like the EA5163/S1709 INSIGNA trial [12], which indirectly matches the intervention evaluated in this study.

Table 1. Clinical Characteristics of Eligible Cases (N (%))

Factors	Immunotherapy			Total	P value
	Yes	Yes	No		
	Starting in				
	0 - 30 days	31 - 60 days	NA		
Total	3,291 (100%)	237 (100%)	4,309 (100%)	7,837 (100%)	
Institution					
Academic	965 (29%)	67 (28%)	1,227 (28%)	2,259 (29%)	0.71
Other	2,326 (71%)	170 (72%)	3,082 (72%)	5,578 (71%)	
Age					
70 and older	1,075 (33%)	83 (35%)	1,573 (37%)	2731 (35%)	< 0.01
Less than 70	2,216 (67%)	154 (65%)	2,736 (63%)	5,106 (65%)	
Sex					
Male	1,838 (56%)	123 (52%)	2,536 (59%)	4,497 (57%)	< 0.01
Female	1,453 (44%)	114 (48%)	1,773 (41%)	3,340 (43%)	
Race					
White	2,789 (85%)	212 (89%)	3,540 (82%)	6,541 (83%)	< 0.01
Other	502 (15%)	25 (11%)	769 (18%)	1,296 (17%)	
CD score					
0 - 1	3,138 (95%)	226 (95%)	4,131 (96%)	7,495 (96%)	0.54
2 - 3	153 (5%)	11 (5%)	178 (4%)	342 (4%)	
Year of diagnosis					
2017	1,164 (35%)	116 (49%)	2,809 (65%)	4,089 (52%)	< 0.01
2018	2,127 (65%)	121 (51%)	1,500 (35%)	3,748 (48%)	
Histology					
Adenocarcinoma	2,785 (85%)	159 (67%)	2,634 (61%)	5,578 (71%)	< 0.01
Other	506 (15%)	78 (33%)	1,675 (39%)	2,259 (29%)	
Clinical T stage					
cT3-4	1,554 (47%)	129 (54%)	2,214 (51%)	3,897 (50%)	< 0.01
Other	1,737 (53%)	108 (46%)	2,095 (49%)	3,940 (50%)	
Clinical N stage					
cN2-3	2,250 (68%)	153 (65%)	2,905 (67%)	5,308 (68%)	0.39
Other	1,041 (32%)	84 (35%)	1,404 (33%)	2,529 (32%)	
Clinical M stage					
cM1BC	2,240 (68%)	162 (68%)	2,790 (65%)	5,192 (66%)	< 0.01
Other	1,051 (32%)	75 (32%)	1,519 (35%)	2,645 (34%)	
Surgery					
Yes	63 (2%)	4 (2%)	69 (2%)	136 (2%)	0.58
No	3,228 (98%)	233 (98%)	4,240 (98%)	7,701 (98%)	
Radiation					
Yes	1,237 (38%)	116 (49%)	1,947 (45%)	3,300 (42%)	< 0.01
No	2,054 (62%)	121 (51%)	2,362 (55%)	4,537 (58%)	
Brain metastasis					
Yes	771 (23%)	52 (22%)	918 (21%)	1,741 (22%)	0.09
No	2,520 (77%)	185 (78%)	3,391 (79%)	6,096 (78%)	
Liver metastasis					
Yes	651 (20%)	49 (21%)	869 (20%)	1,569 (20%)	0.89
No	2,640 (80%)	188 (79%)	3,440 (80%)	6,268 (80%)	

CD: Charlson-Deyo.

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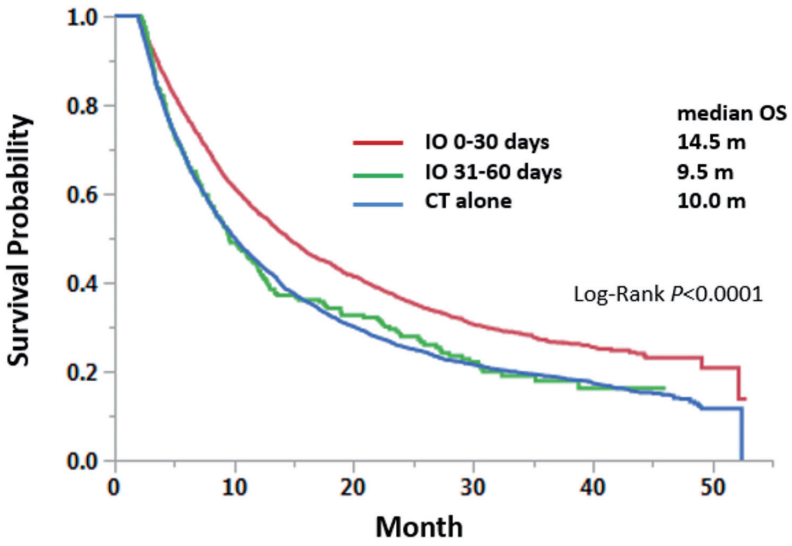
Table 2. Univariate and Multivariable Cox Regression Analyses for Overall Survival in Patients With Stage IV NSCLC Treated With Combination Therapy (Within 30 Days vs. 30 - 61 Days)

Factors	Univariate	Multivariate
	HR (95% CI), P value	HR (95% CI), P value
Institution		
Academic	0.92 (0.84 - 1.01), 0.07	0.94 (0.85 - 1.02), 0.14
Others (reference)		
Age		
< 70	0.79 (0.72 - 0.86), < 0.01	0.78 (0.71 - 0.85), < 0.01
≥ 70 (reference)		
Sex		
Female	0.79 (0.72 - 0.85), < 0.01	0.79 (0.73 - 0.86), < 0.01
Male (reference)		
Race		
Others	0.83 (0.73 - 0.93), < 0.01	0.86 (0.76 - 0.97), 0.01
White (reference)		
CD score		
0 - 1	1.01 (0.84 - 1.23), 0.92	0.95 (0.79 - 1.15), 0.63
≥ 2 (reference)		
Year of diagnosis		
2018	0.99 (0.91 - 1.08), 0.82	1.00 (0.92 - 1.09), 0.99
2017 (reference)		
Histology		
Adenocarcinoma	0.81 (0.73 - 0.90), < 0.01	0.88 (0.79 - 0.99), 0.02
Others (reference)		
Clinical T stage		
Others	0.92 (0.85 - 1.00), 0.05	0.96 (0.88 - 1.04), 0.34
T3-4 (reference)		
Clinical N Stage		
Others	0.83 (0.76 - 0.91), < 0.01	0.83 (0.76 - 0.91), < 0.01
N2-3 (reference)		
Clinical M stage		
Other	0.82 (0.75 - 0.90), <0.01	0.95 (0.86 - 1.04), 0.26
M1BC (reference)		
Surgery		
Yes	0.70 (0.50 - 0.95), 0.02	0.74 (0.53 - 1.03), 0.07
No (reference)		
Radiation		
No	0.84 (0.76 - 0.91), < 0.01	0.82 (0.75 - 0.91), < 0.01
Yes (reference)		
Brain metastasis		
No	0.93 (0.85 - 1.02), 0.13	0.99 (0.88 - 1.10), 0.81
Yes (reference)		
Liver metastasis		
No	0.63 (0.58 - 0.70), < 0.01	0.64 (0.58 - 0.71), < 0.01
Yes (reference)		
Time of immunotherapy		
0 - 30 days	0.74 (0.64 - 0.87), < 0.01	0.78 (0.67 - 0.91), < 0.01
31 - 60 days (reference)		

NSCLC: non-small cell lung cancer; HR: hazard ratio; CI: confidence interval; CD: Charlson comorbidity.

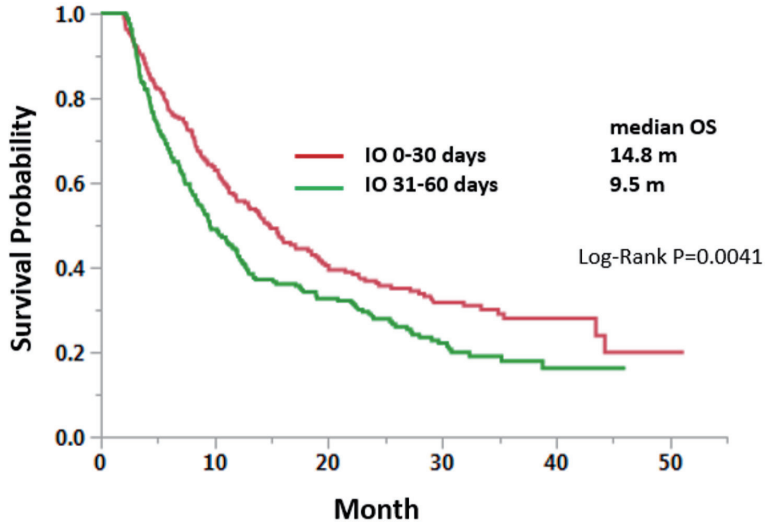


At risk (month)	0	12	24	36	48
CT+IO within 30 days	3291	1671	866	242	18
CT+IO 31-60 days	237	96	49	15	0
CT alone	4309	1763	874	381	45

Figure 2. Immunotherapy within the first 30 days of chemotherapy treatment improves overall survival in patients with stage IV non-small cell lung cancer, compared to delayed or no immunotherapy statuses. Median survival months and log-rank P values are shown. CT: chemotherapy; IO: immunotherapy; OS: overall survival.

It is certainly important to acknowledge some of the limitations inherent in our study. Firstly, the non-randomized assignment of patients to treatment groups, and the retrospective nature of our analysis introduce inherent biases. To mitigate these, PSM and multivariate analyses were employed.

Furthermore, while the NCDB database serves as a valuable resource for cancer-related research, it does not include all the relevant clinical data, such as Eastern Cooperative Oncology Group (ECOG) performance status, disease-free survival, molecular status (e.g., *EGFR* mutation), details on immunotherapy-related adverse events, and concurrent non-cancer medications. Of note, the absence of molecular profiling data



At risk (month)	0	12	24	36	48
CT+IO within 30 days	237	124	65	25	2
CT+IO 31-60 days	237	96	49	15	0

Figure 3. Propensity score matching analysis of early (30 days) and delayed (31 - 60 days) immunotherapy groups. Matched cases were compared for OS. CT: chemotherapy; IO: immunotherapy; OS: overall survival.

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could potentially constrain the generalizability of our findings, particularly given the paramount importance of targeted therapies for individuals harboring driver oncogenes such as *EGFR* and *ALK*. However, it warrants acknowledgment that the representation of such subgroups within the NCDB cohort is relatively modest, constituting approximately 20% of participants, with a predominant demographic skew towards Caucasians.

Additionally, our findings lack external validation from independent cohorts, demonstrating the need for further validation to strengthen the robustness of our results. Moving forward, prospective studies incorporating a more comprehensive array of variables are warranted to enhance the evidential support for our findings.

In conclusion, this retrospective study using one of the largest cancer databases suggests that delaying immunotherapy when used in combination with chemotherapy have detrimental effects on survival outcome and that early introduction of immunotherapy correlates with favorable clinical outcomes.

Supplementary Material

Suppl 1. Characteristic of patients after propensity score matching.

Suppl 2. Univariate and multivariable Cox regression analyses for overall survival in patients with stage IV NSCLC treated with combination therapy: within 30 days vs. 30 - 61 days (propensity score matching analysis).

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Financial Disclosure

Takefumi Komiya received advisory fees from Novocure and Regenerone, and institutional research funding from Gilead.

Conflict of Interest

Takefumi Komiya received advisory fees from Novocure and Regenerone. The other authors declared no financial interest.

Informed Consent

Not applicable.

Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Takefumi Komiya. The first draft of the manuscript was written by Jorge Raul Vazquez-Urrutia, and all authors read and approved the final manuscript.

Data Availability

The datasets analyzed during the current study are available via NCDB upon request.

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