CANCER RESEARCH AND TREATMENT (CRT)

Original Article

Association of Immune-Related Adverse Events and the Efficacy of Anti-PD-(L)1 Monotherapy in Non-Small Cell Lung Cancer: Adjusting for Immortal-Time Bias

Ying Yu[1,2,#], Ning Chen[1,2,#], Sizhe Yu[1], Wanji Shen[1,3], Wanchen Zhai[1,2], Hui Li[1], Yun Fan[1,*]

[1]Department of Thoracic Medical Oncology, Zhejiang Cancer Hospital, Hangzhou Institute of Medicine (HIM), Chinese Academy of Sciences, Hangzhou, Zhejiang, [2]Department of Oncology, The Second Clinical Medical College, Zhejiang Chinese Medical University, Hangzhou, [3]Wenzhou Medical University, Wenzhou, China

[#]Ying Yu and Ning Chen contributed equally to this work.

Correspondence: Yun Fan

Department of Thoracic Medical Oncology, Zhejiang Cancer Hospital, Hangzhou Institute of Medicine (HIM), Chinese Academy of Sciences, No. 1 East Banshan Road, Gongshu District, Hangzhou, Zhejiang 310022, China.

Tel: 86-571-88122091 Fax: 86-571-88122515 E-mail: fanyun@zjcc.org.cn

Accepted Article

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as an 'Accepted Article', doi:10.4143/crt.2023.1118

Korean Cancer Association
This article is protected by copyright. All rights reserved.

Abstract

Purpose

The association between immune-related adverse events (irAEs) and survival outcomes in non-small cell lung cancer (NSCLC) patients treated with programmed-death-(ligand)1 [PD-(L)1] inhibitors remains controversial, partly due to variations in dealing with immortal-time bias (ITB).

Materials and Methods

We retrospectively enrolled 425 advanced NSCLC patients who received anti-PD-(L)1 monotherapy between January 2016 and June 2021, stratifying them into irAE (n=127) and non-irAE (n=298) groups. The primary endpoint was to assess the impact of irAEs on progression-free survival (PFS) and overall survival (OS). Landmark (2-, 3-, 6-, and 9-month) and time-dependent Cox analyses were performed to eliminate ITB.

Results

With a median follow-up of 38.8 months, the occurrence of overall irAEs was significantly associated with superior PFS (11.2 vs. 3.4 months, p<0.0001) and OS (31.4 vs. 14.0 months, p<0.0001), which persisted in landmark and time-dependent Cox analyses. For the main organ-specific irAEs, skin, thyroid, and hepatic irAEs, respectively, showed significantly improved survival compared to the non-irAE group, whereas pneumonitis did not. Single-organ irAEs had the best outcomes compared with multi-organ or no irAE, which also held across subgroups of skin, thyroid and hepatic irAEs. Moreover, severe grade irAEs and immunotherapy discontinuation had a detrimental effect on survival, systemic steroid therapy showed little effect, while immunotherapy resumption had tolerable safety and a trend of improved survival.

Conclusion

After adequately adjusting ITB, the occurrence of overall irAEs predicts for favorable efficacy of anti-PD-(L)1 monotherapy in NSCLC, with better outcomes observed in patients with skin, thyroid, or hepatic irAEs, particularly those with single-organ involvement.

Korean Cancer Association
This article is protected by copyright. All rights reserved.

Accepted Article

Keywords

Non-small cell lung cancer, PD-1/PD-L1 inhibitors, Immune-related adverse events, Therapeutic efficacy, Immortal-time bias

Accepted Article

Korean Cancer Association
This article is protected by copyright. All rights reserved.

Introduction

Immune checkpoint inhibitors (ICIs) targeting programmed-death-(ligand)1 [PD-(L)1] have become the cornerstone of treatment for advanced non-small cell lung cancer (NSCLC). By inhibiting tumor immune evasion, ICIs are able to reactivate antitumor immunity, but their use may also lead to a broad spectrum of immune-related adverse events (irAEs). Mechanically, the generation of irAEs is likely to be linked with destroyed immune tolerance, overactivated lymphocytes, and increased pro-inflammatory cytokines and autoantibodies [1-5], which appears to represent an enhanced antitumor response due to the overactivation of the immune system triggered by ICIs. Therefore, there has been growing concern about whether irAEs could be a predictive clinical biomarker of ICI efficacy.

Previous studies have correlated irAEs with increased ICI efficacy in NSCLC [1,6-8]. Nevertheless, since the development of irAEs is a time-varying covariate that would lead to immortal-time bias (ITB) if analyzed conventionally as a fixed covariate, these studies that did not take this bias into account may have overestimated the survival difference in favor of the irAE group [9]. To eliminate ITB, appropriate statistical methods, such as landmark or time-dependent Cox regression analysis, have been used in multiple studies but have demonstrated conflicting results. For instance, several studies manifested a significantly greater survival benefit in NSCLC patients with irAEs than in those without [10], while others indicated no significant difference in progression-free survival (PFS) or overall survival (OS) between irAE and non-irAE groups [12,13]. Furthermore, this inconsistency was more prominent when both methods were simultaneously applied to limit the bias. Maria et al. detected that the occurrence of irAEs was positively associated with PFS and OS in the time-dependent Cox model, which was absent in the landmark analysis [14]. Conversely, a recent pooled analysis of NSCLC patients from three randomized phase III trials reported that regardless of statistical methods,

Korean Cancer Association
This article is protected by copyright. All rights reserved.
Accepted Article

patients with irAEs had a longer OS than those without irAEs in the atezolizumab arm [15]. In addition, available data have shown that not all specific irAEs are equal in terms of improving ICI response, which is an intricate balance of the integrational effects of irAE characteristics and subsequent management. Different types and numbers of organ-specific irAEs, different grades of irAEs, and different subsequent management strategies, including whether to discontinue or resume ICIs or to use systemic steroids, may selectively exert differing effects (beneficial, harmful, or uncertain) [1,11,15-17], but the evidence has been limited and controversial.

Given the above unresolved questions, we retrospectively investigated the association between irAEs and survival outcomes in advanced NSCLC patients who received anti-PD-(L)1 monotherapy, using appropriate statistical methods to adequately limit ITB. Furthermore, due to the complexity and differing effects of different irAEs, we aimed to further analyze the impact of specific irAEs on survival in real-world settings, especially organ-specific irAEs.

Materials and Methods

1. Patients and data collection

We retrospectively screened 3,139 lung cancer patients who initiated anti-PD-(L)1 therapy at Zhejiang Cancer Hospital between January 2016 and June 2021. The major exclusion criteria were: small-cell lung cancer, participation in clinical trials, receiving PD-(L)1 inhibitors in combination with chemotherapy/antiangiogenic agents/other ICIs, Eastern Corporation Oncology Group performance status (ECOG PS) ≥ 3, and incomplete clinical or follow-up data. Ultimately, 425 patients who had (1) histologically or cytologically confirmed advanced NSCLC, (2) at least one measurable lesion, (3) received anti-PD-(L)1 monotherapy for at least one dose, (4) ECPG PS ≤ 2, and (5) complete clinicopathological and survival data were

Korean Cancer Association
This article is protected by copyright. All rights reserved.
Accepted Article

enrolled. Among these patients, 127 developed irAEs after ICI initiation, but 298 did not. The study flowchart of patient selection is displayed in the S1 Fig.

Data on patient demographics at the initiation of ICIs, irAE characteristics (including the period from ICI initiation to irAE onset, the type and the number of organs involved, and grade) and management (such as ICI discontinuance, systemic steroid therapy, ICI resumption, and irAE recurrence) during ICI treatment were extracted from the medical records of the hospital. This study was approved by the Zhejiang Cancer Hospital's Ethics Committee.

2. Definition of irAEs and assessment of clinical response

IrAEs were definitively diagnosed by two oncologists based on pathological evidence, laboratory tests, radiographic examinations, and even multidisciplinary consultation. We categorized irAEs based on the organ involved as skin toxicity, thyroid dysfunction, pneumonitis, hepatic toxicity, colitis/diarrhoea, pancreatic toxicity, renal toxicity, neuromuscular toxicity, arthritis, myocarditis/arrhythmia, hematologic toxicity, and infusion-related reaction. The irAE onset time was counted as the period from the first ICI administration to the first occurrence of irAEs. The grade of each irAE was evaluated using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, ranging from grade 1 to grade 5. In addition, irAEs involving only 1 organ were defined as "single-organ irAEs", and those involving ≥2 organs were defined as "multi-organ irAEs".

The response to ICIs was evaluated radiographically every 6-8 weeks, according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1). PFS was defined as the period from initiating anti-PD-(L)1 monotherapy until disease progression, death, or the last follow-up. OS was calculated from the first anti-PD-(L)1 administration until death owing to any cause or the last follow-up. These enrolled patients were followed up until December 31, 2022.

Korean Cancer Association
This article is protected by copyright. All rights reserved.
Accepted Article

3. Statistical analysis

The occurrence of irAEs was first analyzed as a fixed covariate, as if all patients were aware of it before follow-up began. However, as the occurrence of irAEs was a time-varying covariate that occurred at some unspecified time-point during follow-up, both landmark and time-dependent Cox regression analyses were used together to limit ITB. We determined landmarks at 2, 3, 6, and 9 months after ICI initiation, including only patients who were progression-free or those who were alive. Then, landmark-based analyses for PFS and OS were performed (patients who experienced irAEs within 2, 3, 6 or 9 months were compared with those without irAEs, respectively; notably, patients developed an irAE after the landmark time were also classified in the non-irAE group). In addition, a time-dependent Cox model was conducted to obtain the adjusted hazard ratio (HR) and 95% confidence interval (95% CI). Patient demographics with a $p < 0.1$ in the univariable Cox regression analysis were included in the final multivariate analysis to adjust for potential confounders related to the effect of irAEs on survival. Similar analyses were subsequently performed for organ-specific subgroups, but restricted to those common irAEs with an incidence of 5% or more (including skin toxicity, thyroid dysfunction, pneumonitis, and hepatic toxicity).

Continuous variables were summarized as medians and ranges, and categorical variables were reported as frequencies and percentages. Baseline clinical characteristics between the irAE and non-irAE groups were compared through the independent t tests and Chi-squared tests. Survival analyses of PFS and OS were estimated by the Kaplan–Meier method, and the differences were tested by the log-rank test. A two-tailed $p < 0.05$ was considered statistically significant. All statistical analyses were conducted with SPSS (version 26.0) and R (ver. 4.2.1).

Accepted Article

Korean Cancer Association
This article is protected by copyright. All rights reserved.

Results

1. Patient demographics

The baseline clinical characteristics of the 425 patients are detailed in Table 1. Among them, the median age was 62 years (range 27-88), 78.1% were male, and 68.7% had a smoking history. The ECOG PS was 0 in 122 patients (28.7%), 1 in 255 patients (60.0%), and 2 in 48 patients (11.3%). Lung adenocarcinoma accounted for 44.0% (n=187), squamous cell carcinomas accounted for 48.7% (n=207), and other NSCLCs accounted for 7.3% (n=31). The numbers of patients who received anti-PD-(L)1 monotherapy as first-line, second-line, and third-line or further line treatment were 84 (19.8%), 229 (53.9%), and 112 (26.3%), respectively. The 425 patients were further categorized into irAE group (n=127) and non-irAE group (n=298). Apart from patients with irAEs experiencing a longer median duration of ICI treatment than those without irAEs (12.0 vs. 4.5 doses, $p < 0.001$), baseline characteristics were generally balanced between the two groups.

2. The incidence, spectrum, and management of irAEs

Overall, a total of 127 patients (29.9%) developed 186 irAEs, where 89 patients presented single-organ irAEs and 38 patients presented multi-organ irAEs with 2 to 6 organs affected. The median time to onset of the first irAEs was 69 (range 0-1265) days. Skin toxicity was the most frequent irAE (42/425, 9.9%), followed by thyroid dysfunction (39/425, 9.2%), pneumonitis (27/425, 6.4%), hepatic toxicity (25/425, 5.9%), and some other relatively small proportion of irAEs et.al. Most patients (100/127, 78.7%) exhibited irAEs of grade 1-2, with relatively few grade 3-5 (27/127, 21.3%) events (Table 2). There were 4 irAE-related deaths, including 3 cases of pneumonitis and 1 case of thrombocytopenia. Due to irAEs, 50 (50/127, 39.4%) patients discontinued ICIs, mostly with pneumonitis; 50 (50/127, 39.4%) patients were treated with

Korean Cancer Association
This article is protected by copyright. All rights reserved.
Accepted Article

systemic steroids, and 8 patients required additional immunosuppressive or biologic agents. In the 14-patient resumption cohort, 8 (57.1%) patients had a recurrence of irAEs, including 5 with the original irAE and 3 with both the original and a new irAE. Most recurrent irAEs were no more severe than the original ones (5/8, 62.5%), comprising 4 cases of grade 1-2 and no irAE-related deaths (S2 Table).

3. Association between overall irAEs and ICI efficacy

In the overall population, without adjusting for ITB, the objective response rate (ORR) was 37.0% for patients with irAEs and 17.8% for those without irAEs ($p < 0.001$), and the disease control rate (DCR) was 89.8% and 65.8% ($p < 0.001$), respectively (S3 Table). With a median follow-up of 38.8 months (95% CI, 34.5-43.1), patients with irAEs exhibited superior PFS (11.2 vs. 3.4 months, $p < 0.0001$) and OS (31.4 vs. 14.0 months, $p < 0.0001$) compared to those without irAEs. When ITB was accounted for, PFS and OS were also significantly longer in patients with irAEs at the 2-month (13.6 vs. 6.7 months, $p < 0.001$; 26.9 vs. 17.1 months, $p=0.004$) and 3-month landmarks (13.6 vs. 9.0 months, $p=0.001$; 27.5 vs. 16.5 months, $p=0.001$), as well as at the 6-month (16.4 vs. 12.8 months, $p=0.001$; 29.0 vs. 20.2 months, $p=0.001$) and 9-month (19.7 vs. 15.8 months, $p=0.021$; 36.8 vs. 23.5 months, $p<0.001$) landmarks (Fig. 1).

4. Impact of different organ-specific irAEs on survival

The number of patients at each landmarks according to the type and number of organs involved is shown in S4 Table in the Supplement. Regarding the common organ-specific irAEs, unadjusted analyses demonstrated that skin, thyroid, and hepatic irAEs were significantly associated with better PFS and OS, while pneumonitis had no statistically significant impact on survival. However, the landmark analysis yielded dramatically heterogeneous results, showing

Korean Cancer Association
This article is protected by copyright. All rights reserved.
Accepted Article

only a significant correlation between PFS and thyroid irAEs at the 2-month (HR=0.49), 3-month (HR=0.52) and 6-month (HR=0.58) landmarks, as well as a significant correlation between OS and skin irAEs at the 3-month landmark (HR=0.62) and thyroid irAEs at the 2-month (HR=0.33) and 3-month (HR=0.48) landmarks (Fig. 2A).

5. Impact of number of organs involved on survival

Patients with single-organ irAEs manifested a prolonged PFS (11.4 vs. 10.4 vs. 3.4 months, p<0.0001) and OS (34.9 vs. 21.1 vs. 14.0 months, p<0.0001) than those with multi-organ or no irAEs, which was also seen at all landmarks (S5 Fig.). Moreover, a further subgroup analysis stratified by the number of organs involved in each common organ-specific irAE showed that the survival advantage of single-organ irAEs persisted across populations with skin, thyroid and hepatic irAEs (Fig. 2B).

6. Impact of irAE grade and management on survival

In addition, patients with grade 1-2 irAEs had longer PFS (11.8 vs. 8.2 vs. 3.4 months, p<0.0001) and OS (34.9 vs. 18.0 vs. 14.0 months, p<0.0001) than those with grade 3-5 or no irAEs. Generally, severe irAEs were advised to be managed with ICI discontinuance and/or systemic steroids according to guidelines. We found that patients who discontinued treatment due to irAEs had worse PFS (9.3 vs. 12.1 months, p=0.03) and OS (20.6 vs. 41.9 months, p=0.046) than those who continued treatment. Systemic steroid therapy had a slight detrimental effect on PFS (10.8 vs. 11.2 months, p=0.03), but the difference in OS did not reach significance (24.2 vs. 32.9 months, p=0.12). After irAEs were resolved, ICI resumption showed a trend towards improved PFS (12.1 vs. 7.9 months, p=0.17) and OS (27.5 vs. 18.0 months, p=0.73) (Fig. 3).

Accepted Article

Korean Cancer Association
This article is protected by copyright. All rights reserved.

7. Time-dependent Cox regression analyses

After adjusting for ITB and potential confounders, we found that overall irAEs were positively correlated with PFS (aHR=0.55; 95% CI, 0.43-0.71; p<0.001) and OS (aHR=0.53; 95% CI, 0.41-0.70; p<0.001). Additionally, similar analyses were performed in subgroups defined by organ-specific irAEs. Skin irAEs were significantly associated with increased PFS (aHR=0.53; 95% CI, 0.36-0.76; p=0.001) and OS (aHR=0.49; 95% CI, 0.31-0.76; p=0.001), as were thyroid irAEs (aHR for PFS=0.58; 95% CI, 0.40-0.86; P=0.006; aHR for OS=0.57; 95% CI, 0.37-0.87; p=0.010). Hepatic irAEs were in related to better OS (aHR=0.49; 95% CI, 0.28-0.86; p=0.013), although had no statistically significant impact on PFS (P=0.067). In contrast to hepatic irAEs, pneumonitis was in association with worse PFS (aHR=1.62; 95% CI, 1.03-2.54; p=0.037) but not with OS (p=0.969) (Table 3).

Discussion

Our study suggests that the presence of overall irAEs was associated with improved survival, which was independent of ITB and potential confounders. Furthermore, patients with skin, thyroid, or hepatic irAEs have better survival benefits, particularly those with single-organ involvement. To our knowledge, this study was the largest cohort study to date specifically focusing on such an association in real-world NSCLC patients receiving anti-PD-(L)1 monotherapy, and it had a longer follow-up than any other previous study.

The incidence of overall irAEs (29.9%) in our study was slightly lower than that in most retrospective studies on NSCLC (28.9% to 51%) [11,12,17-19], which might be attributed to differences in selection criteria that we excluded nonspecific irAEs (such as fatigue, nausea and vomiting) and patients with combination therapy as additional chemotherapy could result in an overestimation of irAEs [20]. The spectrum of irAEs was similar to those previously reported,

Korean Cancer Association
This article is protected by copyright. All rights reserved.
Accepted Article

and no new safety signal was observed. Interestingly, patients who presented with irAEs received more ICI doses than those who did not (median, 12.0 vs. 4.5). This could be interpreted by the significant difference in ORR between the irAE and non-irAE groups (37.0% vs 17.8%), suggesting that patients with irAEs had a greater response to ICI than those without irAEs and therefore received more ICI doses. However, in the non-irAEs group, a significant proportion of patients (19.1%, 57/298) rapidly progressed and even died with only 2 doses of ICI, potentially reducing the duration of treatment in this group. This further adds to the evidence that the occurrence of irAEs could be a predictive clinical biomarker of ICI efficacy.

Regardless of the statistical methods, we observed that the occurrence of irAEs was significantly associated with improved outcomes, similar to most studies using the time-dependent Cox model [10,14,18,20] but contrary to some studies using landmark analysis [12,14]. Such heterogeneous results might be explained by the limitations of the methodology. Landmark analysis excluded patients who experienced early progression and/or death as well as late-onset irAEs, dramatically reducing the sample size and thus impairing statistical power, particularly in small-size analyses. Additionally, the variations in the selection of landmark time points could also strongly influence the results. In most studies, landmark times ranged from 4 weeks to 12 months after ICI initiation. We set the landmarks at 2, 3, 6, and 9 months, aiming to maximize the number of patients developing irAEs while minimizing the number of patients having progression/death prior to the landmarks. The time-dependent Cox analysis adequately included all events and follow-ups since cohort entry, avoiding the two important drawbacks of landmark analysis, so it appeared to be a better methodology to constrain the ITB. Larger prospective studies are warranted to definitively confirm our findings.

Regarding organ-specific irAEs, our results were partially consistent with some retrospective studies [11,14,21,22], suggesting that skin and thyroid irAEs were significantly

Korean Cancer Association
This article is protected by copyright. All rights reserved.
Accepted Article

correlated with ICI efficacy; unlike the controversial relationships [8,13,23], we revealed that hepatic irAEs were associated with better outcomes, while pneumonitis tended to be detrimental. However, why different organ-specific irAEs are related to different outcomes remains unsolved. A possible explanation from a clinical perspective is that different irAE grades and management may have differing effects on survival. Indeed, we noted that grade 1-2 irAEs were associated with superior survival benefits than grade 3-5 or no irAEs and that treatment discontinuation appeared to counteract ICI efficacy, both of which are in line with other studies [15,24,25]. Compared to the other three types of irAEs in our study, pneumonitis exhibited the lowest rate of grade 1-2 (33.3%) and the highest rate of treatment discontinuance (77.8%) and even resulted in 3 deaths; thus, it seemed logical that immune-related pneumonitis could impair survival. This result might be related to the fact that pneumonitis is generally dangerous because of its poorly tolerated hypoxia, particularly in lung cancers that often present with underlying lung damage and limited lung function. In contrast, hepatic irAEs in our study mostly manifested as an increased alanine aminotransferase or aspartate aminotransferase without symptoms or other manifestations, which may be responsible for its positive effect on survival. Altogether, survival differences between different organ-specific irAEs may be attributed to irAE severity and whether treatment was discontinued or not. Alternatively, another assumption from a biological perspective was that organ-specific irAEs might be driven by specific immunopathogenic mechanisms, contributing to distinct responses to ICIs[26,27], which merits further study in detail.

Patients with multi-organ irAEs have previously been shown to have better survival outcomes than those with single-organ or no irAEs [17]. Mechanistically, the development of multi-organ irAEs could be interpreted as ICIs effectively targeting several organs and reflecting a greater antitumor response. However, enhanced immune activation may also be

Korean Cancer Association
This article is protected by copyright. All rights reserved.
Accepted Article

more likely to cause severe irAEs, offsetting the efficacy of ICIs and increasing the risk of death. In our analysis, patients with single-organ irAEs had superior PFS and OS than those with multi-organ or no irAEs. This different result might be attributed to the fact that patients with multi-organ irAEs (12/38, 31.6%) experienced higher rates of grade ≥ 3 irAEs than those with single-organ irAEs (15/89, 16.9%), and even led to 2 deaths. Notably, this survival benefit of single-organ irAEs persisted in subgroups of skin, thyroid, and hepatic irAEs. Insights into mechanisms from basic and translational research are needed.

After severe irAEs are resolved, it may be feasible to resume treatment with ICIs. Simonaggio et al. reported tolerable safety and similar PFS regardless of whether ICIs were resumed or not [28]. Another study by Santini et al. demonstrated a significant improvement in PFS and OS in patients who resumed ICIs, and that subsequent irAEs were mostly mild and manageable [29]. In our study, ICI resumption showed a trend of improved PFS and OS compared to treatment withdrawal, with an acceptable incidence and severity of subsequent irAEs. Overall, ICI resumption appears to be a promising therapeutic option in some patients, but the decision should involve careful balancing of the benefits and risks by physicians. Large prospective trials are warranted to complement the limited available evidence from small-scale retrospective studies.

There were some limitations to our study. First, this was a single-institutional retrospective study. Second, even though two methods, with their own advantages, were applied to eliminate the ITB, they may also create new biases. This is inevitable, but we tried to minimize this bias. Additional limitations include the small subgroup size of patients, especially in the landmark analysis. Finally, it has been hypothesized that the development of irAEs may capture only part of the mechanism of action by which ICIs improve survival, with potential interference from other factors that can affect immune efficacy, such as PD-L1 expression and tumor mutational

Accepted Article

Korean Cancer Association
This article is protected by copyright. All rights reserved.

burden (TMB). However, we were unable to determine the prognostic value of irAEs independently of PD-L1 expression and TMB because both were not routinely tested. Considering these limitations, we should carefully interpret the current results and conduct prospective studies to verify the findings of the association between irAEs and ICI efficacy.

In conclusion, our study indicates that the occurrence of overall irAEs is associated with the efficacy of anti-PD-(L)1 monotherapy in patients with advanced NSCLC after adequately controlling for ITB with landmark and time-dependent Cox analysis. Specifically, certain organ-specific irAEs, such as skin, thyroid, or hepatic irAEs, seem to be associated with better clinical outcomes, particularly in patients with single-organ involvement. In patients experiencing irAEs, the presence of severe grade irAEs and irAE-related treatment discontinuation were related to a detrimental effect on survival, but the use of systemic steroids was not.

Ethics Statement

This retrospective study was approved by the Zhejiang Cancer Hospital's Ethics Committee (Approval No. IRB-2023-682). Informed consent was taken from all patients before participating in any study-related procedure. The study follows the World Medical Association Declaration of Helsinki.

Author Contributions

Conceived and designed the analysis: Yun Fan, Ying Yu.

Collected the data: Ying Yu, Ning Chen, Sizhe Yu, Wanji Shen and Wanchen Zhai; Performed the analysis: Ying Yu, Ning Chen, Sizhe Yu.

Korean Cancer Association
This article is protected by copyright. All rights reserved.
Accepted Article

Wrote the paper: Ying Yu, Ning Chen.

Reviewed the paper: Ying Yu, Hui Li, Yun Fan.

ORCID iDs

Ying Yu: https://orcid.org/0000-0002-3746-5077

Yun Fan: https://orcid.org/0000-0003-1755-0175

Conflicts of Interest

Conflict of interest relevant to this article was not reported.

Acknowledgments

This work was supported by the Natural Science Foundation of China [grant numbers 81972718] and the Natural Science Foundation of Zhejiang Province [grant numbers LY22H160037].

We would like to thank all the members of the Thoracic Medical Oncology of the Zhejiang Cancer Hospital.

Accepted Article

Korean Cancer Association
This article is protected by copyright. All rights reserved.

References

1. Berner F, Bomze D, Diem S, Ali OH, Fässler M, Ring S, et al. Association of Checkpoint Inhibitor-Induced Toxic Effects with Shared Cancer and Tissue Antigens in Non-Small Cell Lung Cancer. JAMA Oncol. 2019;5:1043-7.
2. Toi Y, Sugawara S, Sugisaka J, Ono H, Kawashima Y, Aiba T, et al. Profiling Preexisting Antibodies in Patients Treated with Anti-PD-1 Therapy for Advanced Non-Small Cell Lung Cancer. JAMA Oncol 5:376–83.
3. de Moel EC, Rozeman EA, Kapiteijn EH, Verdegaal EME, Grummels A, Bakker JA, et al. Autoantibody Development under Treatment with Immune-Checkpoint Inhibitors. Cancer Immunol Res. 2019;7:6-11
4. Postow MA, Sidlow R, Hellmann MD. Immune-Related Adverse Events Associated with Immune Checkpoint Blockade. N Engl J Med. 2018;378:158-68.
5. Kang JH, Bluestone JA, Young A. Predicting and Preventing Immune Checkpoint Inhibitor Toxicity: Targeting Cytokines. Trends Immunol. 2021;42:293–311.
6. Rogado J, Sánchez-Torres JM, Romero-Laorden N, Ballesteros AI, Pacheco-Barcia V, Ramos-Leví A, et al. Immune-related adverse events predict the therapeutic efficacy of anti–PD-1 antibodies in cancer patients. Eur J Cancer. 2019;109:21–27.
7. Schweizer C, Schubert P, Rutzner S, Eckstein M, Haderlein M, Lettmaier S, et al. Prospective evaluation of the prognostic value of immune-related adverse events in patients with non-melanoma solid tumour treated with PD-1/PD-L1 inhibitors alone and in combination with radiotherapy. Eur J Cancer. 2020;140:55-62.
8. Teraoka S, Fujimoto D, Morimoto T, Kawachi H, Ito M, Sato Y, et al. Early Immune-Related Adverse Events and Association with Outcome in Advanced Non–Small Cell Lung Cancer Patients Treated with Nivolumab: A Prospective Cohort Study. J Thorac Oncol. 2017;12:1798–805.
9. Giobbie-Hurder A, Gelber RD, Regan MM. Challenges of guarantee-time bias. J Clin Oncol. 2013;31:2963–9.
10. Maillet D, Corbaux P, Stelmes JJ, Dalle S, Locatelli-Sanchez M, Perier-Muzet M, et al. Association between immune-related adverse events and long-term survival outcomes in patients treated with immune checkpoint inhibitors. Eur J Cancer. 2020;132:61-70.
11. Haratani K, Hayashi H, Chiba Y, Kudo K, Yonesaka K, Kato R, et al. Association of Immune-Related Adverse Events With Nivolumab Efficacy in Non-Small-Cell Lung

Korean Cancer Association
This article is protected by copyright. All rights reserved.
Accepted Article

Cancer. JAMA Oncol. 2018;4:374-8.

12. Sato K, Akamatsu H, Murakami E, Sasaki S, Kanai K, Hayata A, et al. Correlation between immune-related adverse events and efficacy in non-small cell lung cancer treated with nivolumab. Lung Cancer. 2018;115:71–4.
13. Fujimoto D, Yoshioka H, Kataoka Y, Morimoto T, Kim YH, Tomii K, et al. Efficacy and safety of nivolumab in previously treated patients with non-small cell lung cancer: A multicenter retrospective cohort study. Lung Cancer. 2018;119:14-20.
14. Kfoury M, Najean M, Lappara A, Voisin AL, Champiat S, Michot JM, et al. Analysis of the association between prospectively collected immune-related adverse events and survival in patients with solid tumor treated with immune-checkpoint blockers, taking into account immortal-time bias. Cancer Treat Rev. 2022;110:102452.
15. Socinski MA, Jotte RM, Cappuzzo F, Nishio M, Mok TSK, Reck M, et al. Association of Immune-Related Adverse Events With Efficacy of Atezolizumab in Patients With Non-Small Cell Lung Cancer: Pooled Analyses of the Phase 3 IMpower130, IMpower132, and IMpower150 Randomized Clinical Trials. JAMA Oncol. 2023;9:527-35.
16. Osorio JC, Ni A, Chaft JE, Pollina R, Kasler MK, Stephens D, et al. Antibody-mediated thyroid dysfunction during T-cell checkpoint blockade in patients with non-small-cell lung cancer. Ann Oncol. 2017;28:583-9.
17. Shankar B, Zhang J, Naqash AR, Forde PM, Feliciano JL, Marrone KA, et al. Multisystem Immune-Related Adverse Events Associated With Immune Checkpoint Inhibitors for Treatment of Non-Small Cell Lung Cancer. JAMA Oncol. 2020;6:1952-6.
18. Lisberg A, Tucker DA, Goldman JW, Wolf B, Carroll J, Hardy A, et al. Treatment-Related Adverse Events Predict Improved Clinical Outcome in NSCLC Patients on KEYNOTE-001 at a Single Center. Cancer Immunol Res. 2018;6:288-94.
19. Wang W, Gu X, Wang L, Pu X, Feng H, Xu C, et al. The prognostic impact of mild and severe immune-related adverse events in non-small cell lung cancer treated with immune checkpoint inhibitors: a multicenter retrospective study. Cancer Immunol Immunother. 2022;71:1693-703.
20. Kurokawa K, Mitsuishi Y, Shimada N, Kawakami Y, Miura K, Miyawaki T, et al. Association between the efficacy and immune-related adverse events of pembrolizumab and chemotherapy in non-small cell lung cancer patients: a retrospective study. BMC Cancer. 2022;22:1047.

Accepted Article

This article is protected by copyright. All rights reserved.

21. Cheung Y-MM, Wang W, McGregor B, Hamnvik O-PR Associations between immune-related thyroid dysfunction and efficacy of immune checkpoint inhibitors: a systematic review and meta-analysis. Cancer Immunol Immunother 2022;71:1795–812.
22. Beaufils M, Amodru V, Tejeda M, Boher JM, Zemmour C, Chanez B, et al. Dysthyroidism during immune checkpoint inhibitors is associated with improved overall survival in adult cancers: data mining of 1385 electronic patient records. J Immunother Cancer. 2023;11:e006786.
23. Suresh K, Psoter KJ, Voong KR, Shankar B, Forde PM, Ettinger DS, et al. Impact of Checkpoint Inhibitor Pneumonitis on Survival in NSCLC Patients Receiving Immune Checkpoint Immunotherapy. J Thorac Oncol. 2019;14:494-502.
24. Naqash AR, Ricciuti B, Owen DH, Florou V, Toi Y, Cherry C, et al. Outcomes associated with immune-related adverse events in metastatic non-small cell lung cancer treated with nivolumab: a pooled exploratory analysis from a global cohort. Cancer Immunol Immunother. 2020;69:1177-87.
25. Verheijden RJ, van Eijs MJM, May AM, van Wijk F, Suijkerbuijk KPM. Immunosuppression for immune-related adverse events during checkpoint inhibition: an intricate balance. NPJ Precis Oncol. 2023;7:41.
26. Esfahani K, Elkrief A, Calabrese C, Lapointe R, Hudson M, Routy B, et al. Moving towards personalized treatments of immune-related adverse events. Nat Rev Clin Oncol. 2020;17:504-15.
27. Henderson Berg M-H, Del Rincón SV, Miller WH. Potential therapies for immune-related adverse events associated with immune checkpoint inhibition: from monoclonal antibodies to kinase inhibition. J Immunother Cancer 2022;10:e003551.
28. Simonaggio A, Michot JM, Voisin AL, Le Pavec J, Collins M, Lallart A, et al. Evaluation of Readministration of Immune Checkpoint Inhibitors After Immune-Related Adverse Events in Patients With Cancer. JAMA Oncol. 2019;5:1310-17.
29. Santini FC, Rizvi H, Plodkowski AJ, Ni A, Lacouture ME, Gambarin-Gelwan M, et al. Safety and Efficacy of Re-treating with Immunotherapy after Immune-Related Adverse Events in Patients with NSCLC. Cancer Immunol Res. 2018;6:1093-9.

Accepted Article

This article is protected by copyright. All rights reserved.

Table 1. Baseline clinical characteristics of patients with advanced NSCLC received PD-1/PD-L1 inhibitors monotherapy.

Characteristics	All patients (n=425)	Patients with irAEs (n=127)	Patients without irAEs (n=298)	p-Value
Median age (range), years	62 (27-88)	63 (27-79)	62 (33-88)	0.878
≤65	272 (64.0)	83 (65.4)	189 (63.4)	0.704
>65	153 (36.0)	44 (34.6)	109 (36.6)	
Sex, n (%)				
Female	93 (21.9)	26 (20.5)	67 (22.5)	0.646
Male	332 (78.1)	101 (79.5)	231 (77.5)	
ECOG PS, n (%)				
0	122 (28.7)	42 (33.1)	80 (26.8)	
1	255 (60.0)	76 (59.8)	179 (60.1)	0.133
2	48 (11.3)	9 (7.1)	39 (13.1)	
Smoking status, n (%)				
Never	133 (31.3)	38 (29.9)	95 (31.9)	0.690
Current or former	292 (68.7)	89 (70.1)	203 (68.1)	
Histology, n (%)				
Adenocarcinoma	187 (44.0)	55 (43.3)	132 (44.3)	
Squamous	207 (48.7)	64 (50.4)	143 (48.0)	0.830
Others	31 (7.3)	8 (6.3)	23 (7.7)	
Stage, n(%)				
III[a]	73 (17.0)	22 (17.3)	51 (16.9)	0.913
IV	356 (83.0)	105 (82.7)	251 (83.1)	
No. of treatment line, n (%)				
1	84 (19.8)	30 (23.6)	54 (18.1)	
2	229 (53.9)	69 (54.3)	160 (53.7)	0.267
≥3	112 (26.3)	28 (22.1)	84 (28.2)	
Type of ICI treatment, n (%)				
PD-1 inhibitors	356 (83.8)	106 (83.5)	250 (83.9)	0.913
PD-L1 inhibitors	69 (16.2)	21 (16.5)	48 (16.1)	
Duration of treatment, doses				
median (range)	6 (2-86)	12 (2-86)	4.5 (2-42)	0.000[b]
Preexisting comorbidities[c], n (%)				
autoimmune disease	8 (1.9)	2 (1.6)	6 (2.0)	0.757
baseline lung disease	37 (8.7)	16 (12.6)	21 (7.0)	0.063
chronic viral infection	41 (9.6)	16 (12.6)	25 (8.4)	0.179

irAEs, immune-related adverse events; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ICI, immune checkpoint inhibitor; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1. [a)]includes patients with recurrent or unresectable stage III NSCLC. [b)]means that the p-value is statistically significant. [c)]Regarding the preexisting comorbidities, autoimmune disease includes hyperthyroidism, gout and rheumatoid arthritis, baseline lung disease consists of chronic obstructive pulmonary disease, mild interstitial pneumonitis, asthma and tuberculosis, and chronic viral infection contains HAV, HBV and EBV virus infection.

Accepted Article

Korean Cancer Association
This article is protected by copyright. All rights reserved.

Table 2. IrAEs spectrum according to the involved organs

IrAEs[a]	Median time of irAEs onset (range), days	Patients with irAEs, No. (%)						
		Total (n=425)	G1-2	G3-5	Systemic steroid	Discontinuance	Resumption	Recurrence
All irAEs	69 (0-1265)	127 (29.9)	100	27	50	50	14	6
Skin toxicity	38.5 (1-439)	42 (9.9)	37	5	8	7	2	1
Thyroid dysfunction	63 (22-392)	39 (9.2)	39	0	0	2	2	1
Pneumonitis	91 (21-828)	27 (6.4)	18	9	25	21	5	2
Hepatic toxicity	104 (20-1265)	25 (5.9)	18	7	9	12	1	0
Diarrhea/colitis	105 (1-525)	7 (1.6)	6	1	3	3	1	0
Pancreatic toxicity	110 (25-501)	5 (1.2)	2	3	0	0	0	0
Neuromuscular toxicity	144 (10-365)	5 (1.2)	5	0	1	0	0	0
Arthritis	270 (10-442)	4 (0.9)	3	1	1	1	0	0
Myocarditis/arrhythmia	190 (45-396)	6 (1.4)	6	0	2	3	2	1
Renal toxicity	74 (14-337)	10 (2.3)	9	1	2	2	1	1
Hematologic toxicity	83 (9-439)	9 (2.1)	8	1	3	3	0	0
Infusion-related reaction	3 (0-26)	7 (1.6)	7	0	0	0	0	0

irAEs, immune-related adverse events; G, grade. [a)]Skin toxicity includes pruritus, rash or both. Thyroid dysfunction includes hypothyroidism and hyperthyroidism. Hepatic toxicity includes increased alanine aminotransferase or aspartate aminotransferase, bilirubin levels, and hepatitis. Pancreatic toxicity includes asymptomatic lipase elevation. Hematologic toxicity included anemia, thrombocytopenia, and granulocytopenia.

Accepted Article

Korean Cancer Association
This article is protected by copyright. All rights reserved.

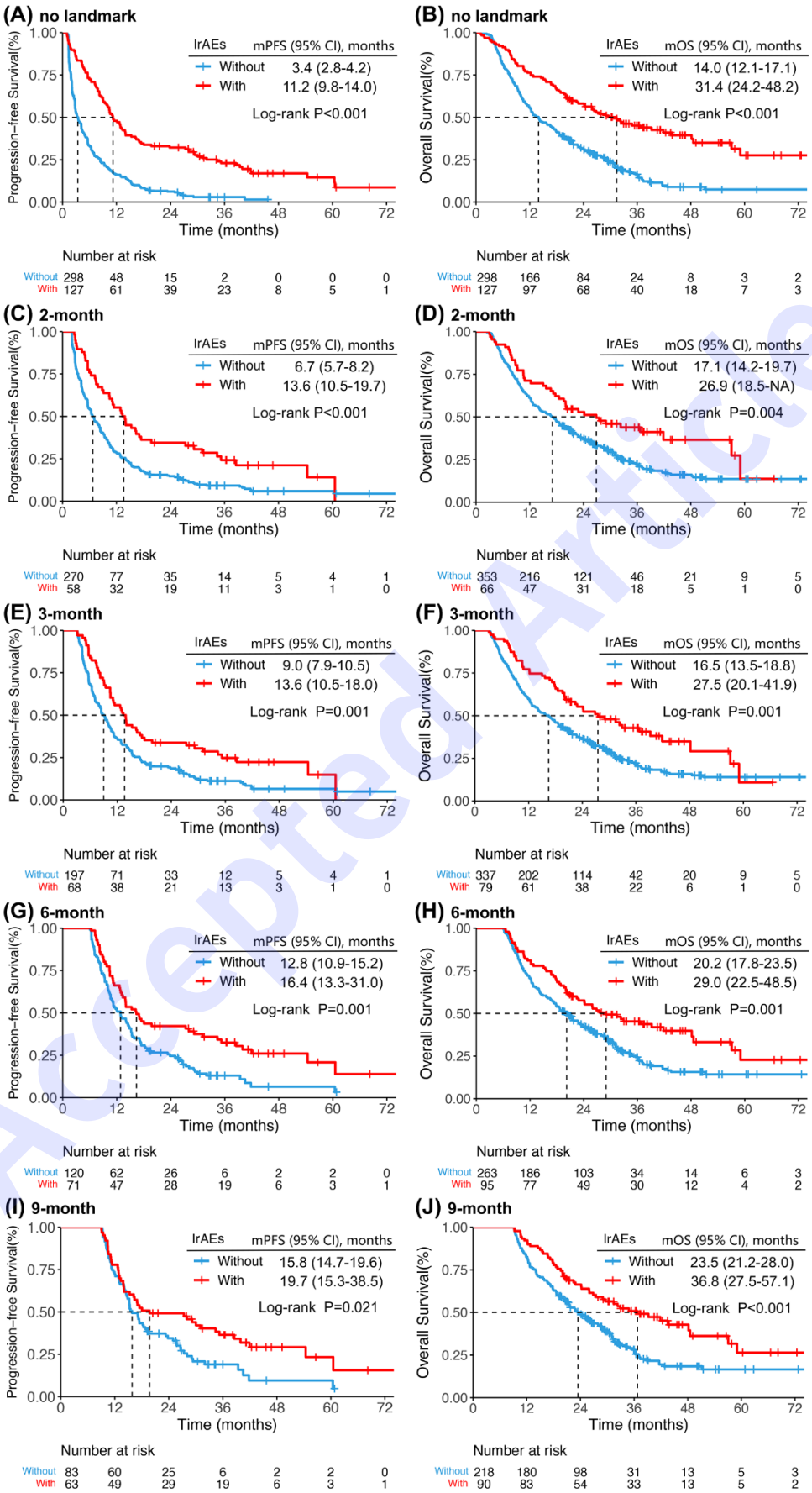
Table 3. Time-dependent Cox regression analyses of the development of irAEs on survival

Survival	Univariate analysis		Multivariate analysis[a)]	
	HR (95% CI)	P	HR (95% CI)	P
Progression-Free Survival				
Overall irAEs (no*, yes)	0.58 (0.45-0.74)	<0.001	0.55 (0.43-0.71)	<0.001
Skin toxicity (no*, yes)	0.60 (0.42-0.87)	0.006	0.53 (0.36-0.76)	0.001
Thyroid dysfunction (no*, yes)	0.60 (0.41-0.89)	0.010	0.58 (0.40-0.86)	0.006
Pneumonitis (no*, yes)	1.53 (0.99-2.37)	0.054	1.62 (1.03-2.54)	0.037
Hepatic toxicity (no*, yes)	0.66 (0.41-1.06)	0.083	0.64 (0.40-1.03)	0.067
Overall Survival				
Overall irAEs (no*, yes)	0.51 (0.39-0.67)	<0.001	0.53 (0.41-0.70)	<0.001
Skin toxicity (no*, yes)	0.49 (0.31-0.75)	0.001	0.49 (0.31-0.76)	0.001
Thyroid dysfunction (no*, yes)	0.57 (0.37-0.87)	0.010	0.57 (0.37-0.87)	0.010
Pneumonitis (no*, yes)	1.01 (0.63-1.63)	0.969		
Hepatic toxicity (no*, yes)	0.49 (0.28-0.86)	0.013	0.53 (0.30-0.93)	0.026

irAEs, immune-related adverse events; HR, hazard ratio; CI, confidence interval. [a)]Covariables included age (≤65 vs. > 65 y), gender (female vs. male), ECOG PS (0 vs. 1 vs. 2), smoking status (never vs. current or former), histology (adenocarcinoma vs. squamous vs. others), stage (III vs. IV), the number of treatment lines (1 vs. 2 vs. ≥2), type of ICI treatment (PD-1 inhibitors vs. PD-L1 inhibitors), duration of ICI treatment, preexisting comorbidities (no vs. yes).

Accepted Article

Korean Cancer Association
This article is protected by copyright. All rights reserved.



Accepted Article

Korean Cancer Association
This article is protected by copyright. All rights reserved.

Fig. 1. Kaplan-Meier curves illustrating the progression-free survival (PFS) and overall survival (OS) in overall patients with and without irAEs from no (A and B), 2-month (C and D), 3-month (E and F), 6-month (G and H), and 9-month (I and J) landmark analyses.

Accepted Article

Korean Cancer Association
This article is protected by copyright. All rights reserved.

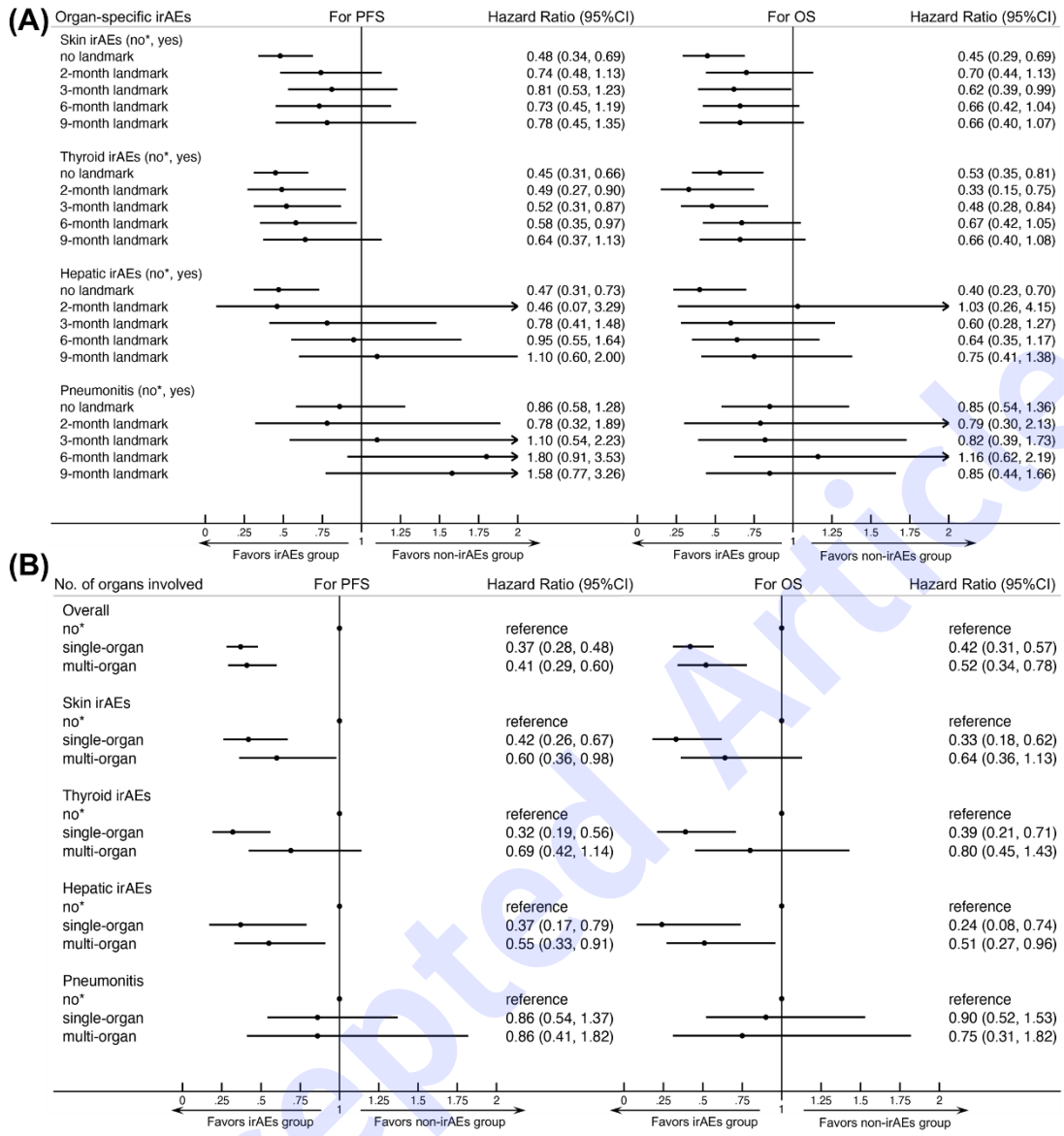


Fig. 2. Forest plots for the impact of different irAE type and number on progression-free survival (PFS) and overall survival (OS). (A) The impact of different type of organ-specific irAEs (including skin irAEs, thyroid irAEs, hepatic irAEs, and pneumonitis) on PFS and OS, with conventional analysis and 2-, 3-, 6-, 9-month landmark analyses. (B) The impact of different number of organs involved by irAEs (no, single-organ, and multi-organ) on PFS and OS in overall and each different organ-specific irAEs groups.

Accepted Article

Korean Cancer Association
This article is protected by copyright. All rights reserved.

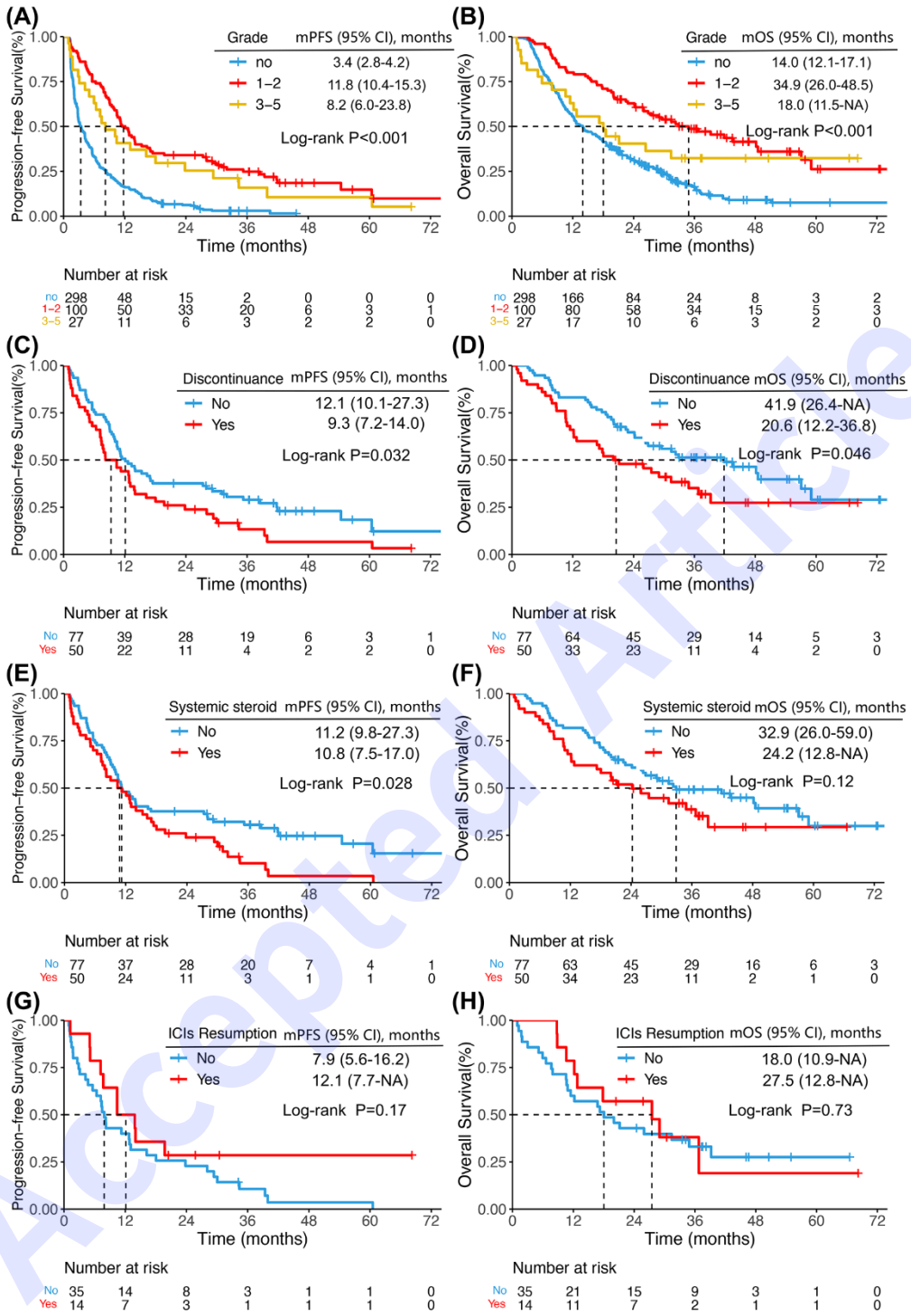
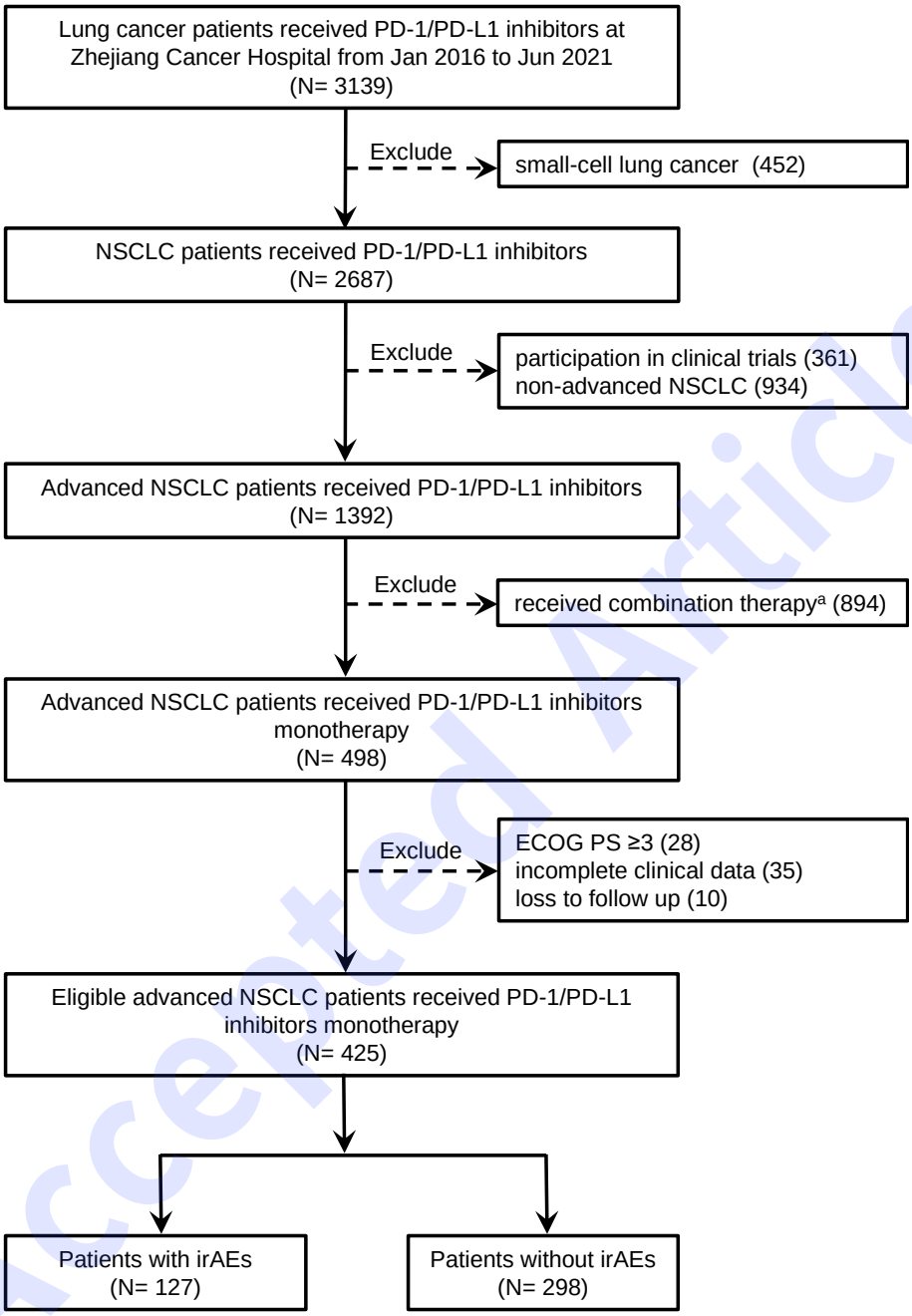


Fig. 3. Kaplan-Meier curves for progression-free survival (PFS) and overall survival (OS) based on irAE grade and managements (no landmark analysis). (A) PFS and (B) OS in patients without, with grade 1-2 or grade 3-5 irAEs. (C) PFS and (D) OS in patients discontinuing ICIs or not. (E) PFS and (F) OS in patients receiving systemic steroid or not. (G) PFS and (H) OS in patients resuming ICIs or not.

Korean Cancer Association
This article is protected by copyright. All rights reserved.



S1 Fig. The study flowchart of patient selection. PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; irAEs, immune-related adverse events; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ICIs, immune checkpoint inhibitors. [a)]combination therapy includes anti-PD-(L)1 monotherapy in combination with chemotherapy/antiangiogenic agents/other immune checkpoint inhibitors.

Korean Cancer Association
This article is protected by copyright. All rights reserved.

S2 Table. IrAEs spectrum in patients with ICI resumption

	Initial irAEs		Time from discontinuation to resumption, days	Subsequent irAEs	
	Type	Grade		Type	Grade
1	Myocarditis	2	25	Myositis/Colitis	1/1
2	Hyperthyroidism	2	50	Hyperthyroidism/ Renal toxicity	2/1
3	Rash/pruritus	3	25	/	/
4	Pneumonitis	2	81	Pneumonitis	3
5	Colitis	3	45	/	/
6	Rash/pruritus	3	169	Rash/pruritus	3
7	Pneumonitis	2	46	Pneumonitis/Liver enzyme elevation	1/4
8	Liver enzyme elevation	3	20	Liver enzyme elevation	1
9	Pneumonitis	2	44	/	/
10	Pneumonitis	2	21	Pneumonitis	2
11	Hyperthyroidism	2	20	/	/
12	Renal toxicity	2	18	Renal toxicity	3
13	Pneumonitis	2	28	/	/
14	Myocarditis	2	121	/	/

irAEs, immune-related adverse events.

Accepted Article

Korean Cancer Association
This article is protected by copyright. All rights reserved.

S3 Table. The efficacy of PD-1/PD-L1 inhibitors monotherapy in advanced NSCLC patients

	Total (n=425)	**With irAEs (n=127)**	**Without irAEs (n=298)**	**P-value**
CR, n(%)	1 (0.2)	1 (0.8)	0 (0)	
PR, n(%)	99 (23.3)	46 (36.2)	53 (17.8)	
SD, n(%)	210 (49.4)	67 (52.8)	143 (48.0)	
PD, n(%)	115 (27.1)	13 (10.2)	102 (34.2)	
ORR, n(%)	100 (23.5)	47 (37.0)	53 (17.8)	0.000
DCR, n(%)	310 (72.9)	114 (89.8)	196 (65.8)	0.000

irAEs, immune-related adverse events; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate.

Accepted Article

Korean Cancer Association
This article is protected by copyright. All rights reserved.

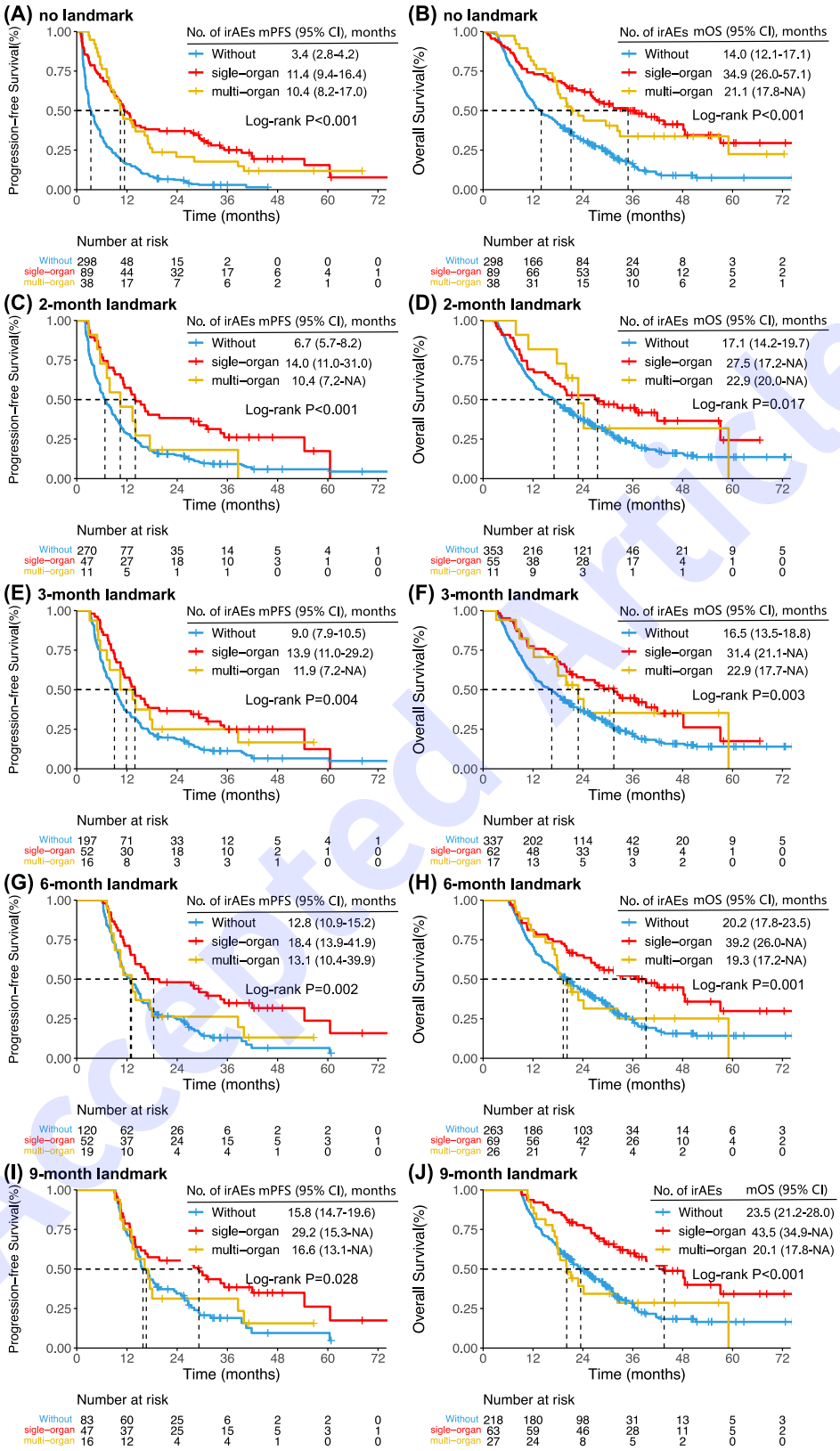
S4 Table. Number of patients at each landmarks according to overall, and different types and numbers of organs involved

Landmarks (patients, N)	no (N=425)	Progression-free survival				Overall survival			
		2-month (N=328)	3-month (N=265)	6-month (N=191)	9-month (N=146)	2-month (N=419)	3-month (N=416)	6-month (N=358)	9-month (N=308)
Overall irAEs, n (%)	127 (29.9)	58 (17.7)	68 (25.7)	71 (37.2)	63 (43.2)	66 (15.8)	79 (19.0)	95 (26.5)	90 (29.2)
The type of organ involved, n (%)									
Skin	42 (9.9)	26 (7.9)	30 (11.3)	25 (13.1)	21 (14.4)	28 (6.7)	32 (7.7)	35 (9.8)	34 (11.0)
Thyroid	39 (9.2)	16 (4.9)	22 (8.3)	26 (13.6)	23 (15.8)	16 (3.8)	25 (6.0)	34 (9.5)	31 (10.1)
Pneumonitis	27 (6.4)	5 (1.5)	8 (3.0)	9 (4.7)	8 (5.5)	6 (1.4)	9 (2.2)	12 (3.4)	13 (4.2)
Hepatic	25 (5.9)	2 (0.6)	11 (4.2)	15 (7.9)	13 (8.9)	3 (0.7)	11 (2.6)	18 (5.0)	18 (5.8)
The number of organs involved, n (%)									
0	298 (70.1)	270 (82.3)	197 (74.3)	120 (62.8)	83 (56.8)	353 (84.2)	337 (81.0)	263 (73.5)	218 (70.8)
1	89 (20.9)	47 (14.3)	52 (19.6)	52 (27.2)	47 (32.2)	55 (13.1)	62 (14.9)	69 (19.2)	63 (20.4)
≥2	38 (9.0)	11 (3.4)	16 (6.1)	19 (10.0)	16 (11.0)	11 (2.7)	17 (4.1)	26 (7.3)	27 (8.8)

irAEs, immune-related adverse events.

Accepted Article

Korean Cancer Association
This article is protected by copyright. All rights reserved.



S5 Fig. Kaplan-Meier curves for progression-free survival (PFS) and overall survival (OS) according to the number of organs involved.

Korean Cancer Association
This article is protected by copyright. All rights reserved.