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Immune-related adverse events with immune checkpoint inhibitors

Special reference to the effects on the lungs

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Abstract

Immune checkpoint inhibitors (ICIs) have emerged as evolutionary treatments for malignant diseases. Although ICIs can cause immune-related adverse events (irAEs) in various organs, precise timing after ICI initiation has been scarcely reported. Elucidating the effects of irAEs, such as time to onset, involvement of major organs, influence on progression-free survival (PFS), and overall survival (OS), are critical issues for physicians. Furthermore, lung-irAE as a whole is not well known.

We conducted a retrospective study of 156 patients who were treated with ICIs and compared 82 irAE patients with 74 non-irAE patients.

This study clearly demonstrated that the preferred period after induction of ICIs was significantly longer in lung-irAE than in other major organs (skin, digestive tract, and endocrine). The effect of irAEs on PFS and OS was evident PFS in the irAE group (n = 82) (median 128 days, interquartile range [IQR] 62–269 days, $P = .002$) was significantly longer than that in the non-irAE group (n = 74) (median 53 days, IQR 33–151 days). Similarly, OS was significantly longer in the irAE group (median 578 days, IQR 274–1027 days, $P = .007$) than in the non-irAE group (median 464 days, IQR: 209–842 days). However, this positive effect of irAEs in the lungs was not proportional to the extent of severity.

Lung-irAEs can occur at a later phase than non-lung-irAEs and seemed not to prolong OS and PFS. However, further studies are needed to support these findings.

Abbreviations: CR = complete remission, CTLA-4 = cytotoxic T-lymphocyte antigen 4, ICIs = immune checkpoint inhibitors, IQR = interquartile range, irAEs = immune-related adverse events, OS = overall survival, PD = progressive disease, PD-1 = programmed death-1, PD-L1 = programmed death-ligand 1, PFS = progression-free survival, PS = performance status, SD = stable disease.

Keywords: immune checkpoint inhibitor, immune-related adverse events, lung toxicity

1. Introduction

In the modern era, immune checkpoint inhibitors (ICIs; nivolumab, pembrolizumab, ipilimumab, and atezolizumab) have emerged as evolutionary treatments in cancer patients. However, the precise time of onset of immune-related adverse events (irAEs) in each organ is not precisely known. In the lung parenchyma, for example, the influence of an irAE on the survival probability or progression-free survival and its relationship with the severity of lung toxicity has been scarcely reported so far. Here, we studied the effects of irAEs in the lungs.

2. Materials and methods

We retrospectively enrolled all patients who received ICIs from February 2016 to October 2019 at Kyorin University, a tertiary center with 1100 beds located in west Tokyo. These patients were all treated with at least one of the following ICIs: nivolumab, pembrolizumab, and atezolizumab.

Throughout the study period, a total number of 156 patients were enrolled in this study. IrAE was defined according to a previous study[1] as an adverse effect with potential immunological reactions. We retrieved the data of irAE patients derived from

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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major organs such as the skin, lung, endocrine glands, digestive tract, and other organs. This study was approved by the Ethics Board of Kyorin University (approval number 1509).

2.1. Clinical characteristics of irAE patients

We compared the data between the irAE group and non-irAE group with respect to age, sex, performance status (PS), disease stage, pathological type, extent of programmed death-ligand 1 (PD-L1) expression (%) in the tumor cells, smoking status, treatment regimens, and number of administrations. Treatment response between the irAE group and non-irAE group was evaluated together with progression-free survival (PFS) and overall survival (OS).

2.2. Evaluation of the effects of all irAEs

We examined the cumulative incidence of irAEs in all enrolled patients and the proportion of organ-based irAEs, as well as the required time after initiation of ICIs. The role of irAEs was analyzed with respect to OS and PFS. Treatment response of irAE patients between sole and multiple organ involvement was evaluated. The effect of irAEs on PFS and OS was also assessed according to the different types of lung cancer.

2.3. Special reference to the role of irAE in the lung

We specifically focused on the role of irAEs in the lung with respect to PFS or OS and its relationship with the severity of lung involvement.

2.4. Statistical analysis

Statistical comparisons of nonparametric data were performed using the Mann–Whitney test or Wilcoxon signed-rank test. Categorical data were compared using Pearson's chi-square test. Categorical data are presented as percentages of the total or as whole numbers, as appropriate. PFS and OS were evaluated between various factors using the Kaplan–Meier method. The log rank test was used to statistically compare the curves and *P* values. All tests were two-sided. A *P*-value $< .05$ was considered statistically significant. Data were analyzed using SPSS version 25.0 software for Windows.

3. Results

3.1. Clinical characteristics of irAE patients

3.1.1. Comparison of the data between the irAE group and non-irAE group. We identified a total of 156 patients, comprising 82 irAE patients (52.6%) and 74 non-irAE patients (47.4%). Age, sex, PS, disease stage, pathological type, extent of PD-L1 expression on the tumor cells (%), smoking status, treatment regimens, and number of administrations were comparable between the 2 groups (Table 1). The treatment regimens were nivolumab (n = 74), pembrolizumab (n = 54), pembrolizumab plus chemotherapy (n = 22), atezolizumab (n = 13), and atezolizumab plus chemotherapy (n = 3), in this order (Table 1). The ratio of administration of ICIs was comparable between the 1st and 2nd treatments between the irAE and non-irAE groups.

Table 1

Patient background.

	irAE	Non-irAE	*P*
Number of patients	82 (52.6)	74 (47.4)	
Age (median, IQR)	69 (62.8–72.0)	70 (58.8–74.0)	.862
Gender			
Male	59 (72.0)	52 (70.3)	.861
PS			
0–1	73 (89.0)	63 (85.1)	.480
2–4	9 (11.0)	11 (14.9)	.480
Stage			
3	24 (29.3)	24 (32.4)	.728
4	56 (68.3)	48 (64.9)	.864
Recurrence	2 (2.4)	2 (2.7)	1.0
Pathological type			
Adeno	53 (64.6)	45 (60.8)	.740
Squamous	25 (30.5)	20 (27.0)	.724
NSCLC	3 (3.7)	7 (9.5)	.194
Other	1 (1.2)	2 (2.7)	.602
PS-L1; TPS			
<50%	30 (36.6)	21 (28.4)	.311
1–49%	14 (17.0)	15 (20.3)	.681
<1%	33 (40.2)	26 (35.1)	.620
NA	5 (6.1)	12 (16.2)	.069
Smoking			
Ex/current	70 (85.4)	66 (89.2)	.632
Never	12 (14.6)	8 (10.8)	.632
Regimen			
Nivolumab	40 (48.8)	34 (45.9)	.750
Pembrolizumab	25 (30.5)	29 (39.2)	.312
Pembrolizumab + chemotherapy	16 (19.5)	6 (8.1)	.064
Atezolizumab	4 (4.9)	9 (12.2)	.146
Atezolizumab + chemotherapy	1 (1.2)	2 (2.7)	.604
Timing of ICIs administration			
1st	21 (25.6)	21 (28.4)	.721
≧2nd	61 (74.4)	53 (71.6)	.721

IQR = interquartile range, irAE = immuno-related adverse events, NA = not available, NSCLC = non-small cell lung carcinoma, PS = performance status, TPS = tissue proportion score. Each parenthesis is described as percent.

3.2. Treatment response in either groups with or without irAE

No patient achieved complete remission (CR) in either group; meanwhile, a significant proportion of the patients in the irAE group showed PR (30.5%, n = 25, $P = .002$) compared to the non-irAE group (5%, n = 7). The proportion of stable disease (SD) was comparable in both groups, but the ratio of progressive disease (PD) was significantly higher in the non-irAE group (52.7%, n = 39) than in the irAE group (29.3%, n = 24, $P = .001$) (Table 2), suggesting a beneficial effect of ICIs.

3.3. Evaluation of the effects of all irAEs

3.3.1. Cumulative incidence of irAE after initiation of treatment with ICIs. The cumulative incidence of irAE after initiation of ICIs showed that the required median time for irAE was 133 days (95% CI: 52–214 days) and the incidence of irAE seemed to be low after 300 days (Fig. 1).

3.3.2. Proportion of irAE in each organ and the timing of irAE in various organs after ICIs. The total number of irAEs was 82 in 82 patients. Major organs with a high incidence of irAEs were the lung (24%, 20 events), endocrine glands (21%, 17 events), skin (15%, 12 events), and digestive tract (9%, 7 events) in this order (Fig. 2A). Other irAEs were recognized in the skin/endocrine (7%, 6 events), lung/endocrine (7%, 6 events), lung/skin (6%, 5 events), and other organs (11%, 9 events) (Fig. 2A). Required time for irAEs differed in major organs (Fig. 2B).

Table 2

Treatment response with or without irAE.

Response	irAE (n = 82)	Non-irAE (n = 74)	*P*
CR	0	0	NS
PR	30.5% (25)	5% (7)	.002
SD	40.2% (33)	37.9% (28)	.626
PD	29.3% (24)	52.7% (39)	.001

CR = complete remission, irAE = immune-related adverse events, NS = not significant, PD = progressive disease, PR = partial response, SD = stable disease.

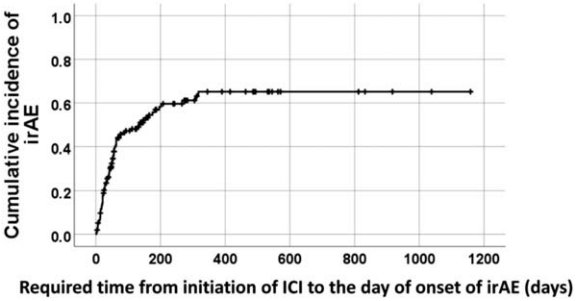

Figure 1. Cumulative incidence of irAE after initiation of the ICI treatment.

Interestingly, lung-irAE showed a significantly longer time (median 204 days, interquartile range [IQR]: 95–642 days) compared to irAEs in the skin (median 29 days, IQR: 14–89 days, $P < .001$), endocrine (median 37 days, IQR: 21–70 days, $P < .001$), and digestive tract (median 29 days, IQR: 8–112 days, $P < .001$) (Fig. 2B). The required time for irAE was comparable in the latter 3 groups (median 29 days, IQR: 17–87 days), suggesting that lung-irAE significantly preferred the late phase ($P < .001$) than in other major organs.

3.3.3. Combination of irAE and treatment response of irAE patients between sole and multiple organ involvement. The proportion of lung irAEs was lung only (n = 20) and lung plus other organs (n = 16). The combination of the latter group was lung (L)/endocrine (E) (n = 6), L/skin (S) (n = 5), L/S/digestive tract (D) (n = 2), L/D (n = 1), L/E/S (n = 1), and L/E/D (n = 1). The proportion of endocrine irAEs was endocrine only (n = 17) and endocrine plus other organs (n = 17), which consisted of E/S (n = 6), E/L (n = 6), E/D (n = 1), E/L/S (n = 1), E/S/D (n = 1), E/L/D (n = 1). Regarding skin irAEs, the number of irAEs involving the skin only and skin plus other organs was 12 and 16, respectively. The latter group consisted of S/E (n = 6), S/L (n = 5), S/L/D (n = 2), S/D (n = 1), S/L/E (n = 1), S/E/D (n = 1). Involvement of only the digestive tract was observed in 7 patients, whereas involvement of the digestive tract plus other organs was observed in 8 patients. The latter group consisted of D/E (n = 2), D/L/S (n = 2), D/S (n = 1), D/L(n = 1), D/E/S (n = 1), and D/E/L (n = 1).

Response to treatment of irAE patients was comparable between sole and multiple organ involvement in the lung (Supplemental Table 1, http://links.lww.com/MD/F971), endocrine (Supplemental Table 2, http://links.lww.com/MD/F972), skin (Supplemental Table 3, http://links.lww.com/MD/F973), and digestive tract (Supplemental Table 4, http://links.lww.com/MD/F974).

3.3.4. PFS and OS with or without irAE. The effect of irAEs on PFS and OS was evident by the Kaplan–Meier method. PFS in the irAE group (n = 82) (median 128 days, IQR 62–269 days, $P = .002$) was significantly higher than that in the non-irAE group (n = 74) (median 53 days, IQR 33–151 days) (Fig. 3A). Similarly, OS was significantly longer in the irAE group (median 578 days, IQR 274–1027 days, $P = .007$) than in the non-irAE group (median 464 days, IQR: 209–842 days) (Fig. 3B).

When we specifically focused on the different types of lung cancer (adenocarcinoma or squamous carcinoma) based on the effects of irAE, the Kaplan–Meier method showed that PFS in the adenocarcinoma group was significantly longer in the irAE

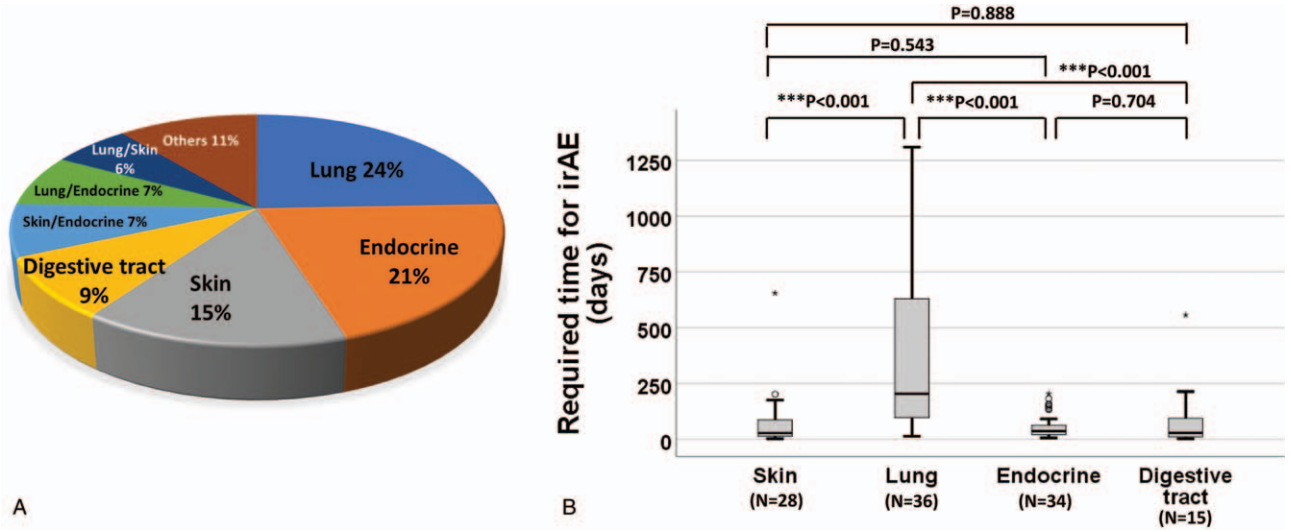

Figure 2. Proportion of irAE showed that the major organs of irAE were the lung (24%), endocrine glands (21%), skin (15%), and digestive tract (9%) in this order (A). The required time for lung-irAE (median 204 days, IQR: 95–642 days) after initiation of ICIs was significantly longer than in other major organs such as the skin (median 29 days, IQR: 14–89 days, $P < .001$), endocrine glands (median 37 days, IQR: 21–70 days, $P < .001$), and digestive tract (median 29 days, IQR: 8–112 days, $P < .001$) (B).

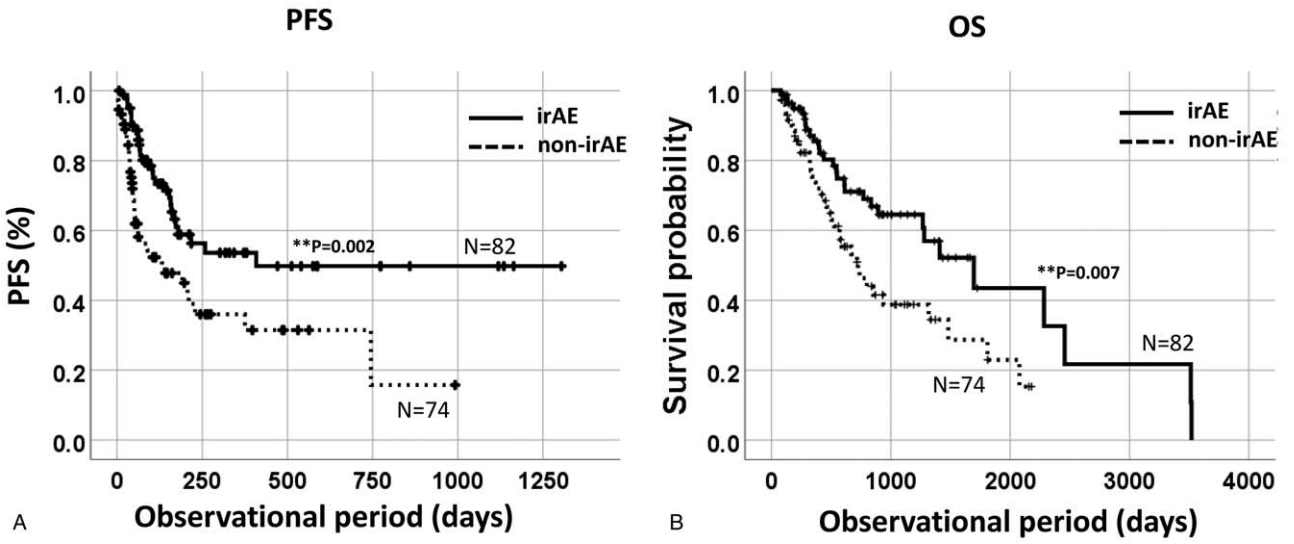

Figure 3. By Kaplan–Meier analysis, among all enrolled patients, irAE patients (n = 82) had a significantly longer progression-free survival (median 128 days, IQR 62–269 days, $P = .002$) than non-irAE patients (n = 74) (median 53 days, IQR 33–151 days) (A). The overall survival was significantly longer in the irAE group (median 578 days, IQR 274–1027 days, $P = .007$) than in the non-irAE group (median 464 days, IQR: 209–842 days) (B).

(n = 53) than in the non-irAE group (n = 45, $P = .022$) (Fig. 4A), but not for OS (Fig. 4B). Regarding squamous carcinoma, PFS was comparable between irAE (n = 25) and non-irAE patients (n = 20) (Fig. 4C), but the OS was significantly longer in the irAE group than in the non-irAE group ($P = .007$) (Fig. 4D).

3.4. Special reference to the role of irAE in the lung

3.4.1. Progression-free survival in all irAE patients with or without lung-irAE after initiation of the ICIs treatment. Among all enrolled patients, PFS on Kaplan–Meier survival between the lung-irAE group (n = 36) and non-lung-irAE group (n = 120) was

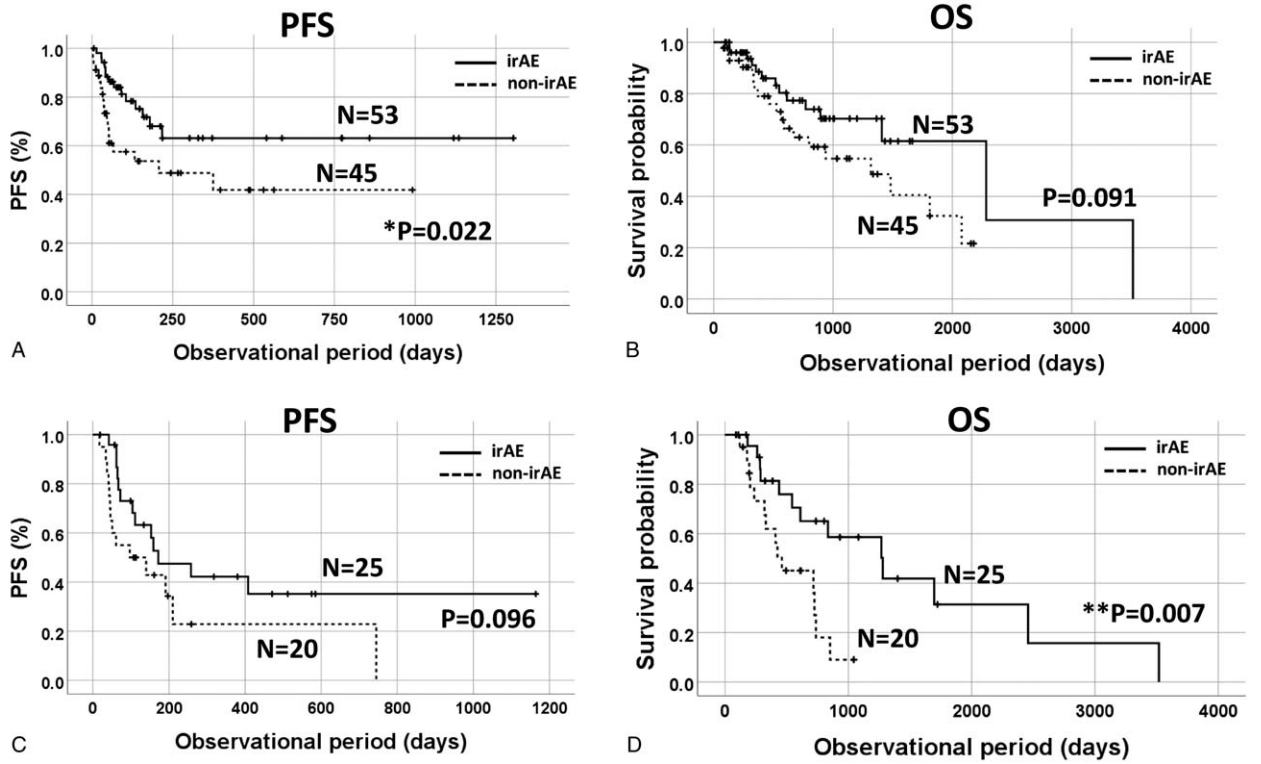

Figure 4. Using the Kaplan–Meier method, comparison of the PFS according to the presence of irAE on adenocarcinoma was significantly longer in the irAE group (n = 53, $P = .022$) than in the non-irAE group (n = 43) (A) but was not statistically significant in OS (B) ($P = .091$). Regarding squamous cell lung cancer, the PFS was not statistically significant between the irAE (n = 25) (C) and non-irAE groups (n = 20, $P = .096$), but the OS was significantly longer in the irAE ($P = .007$) than in the non-irAE group (D).

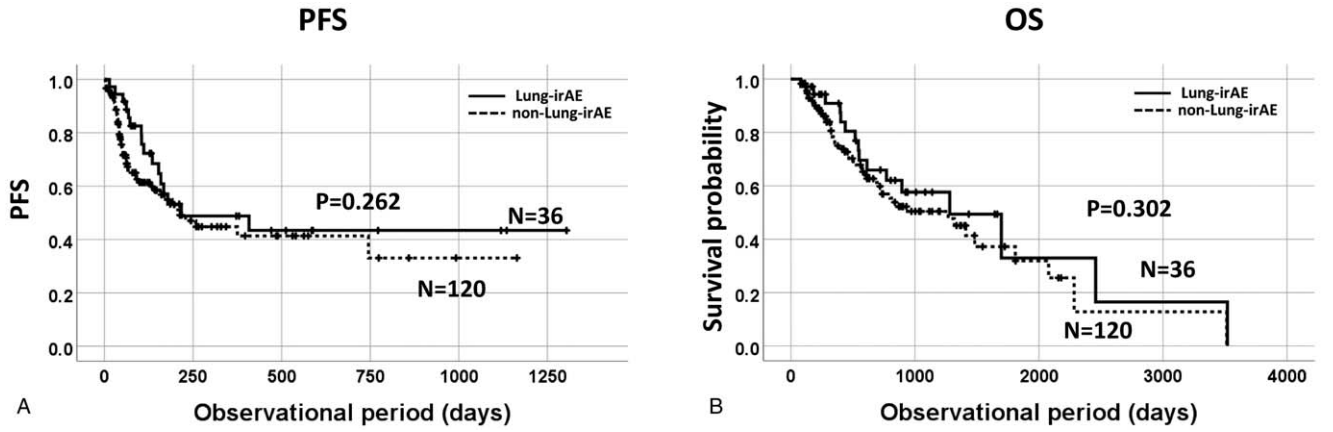

Figure 5. Using the Kaplan–Meier method, comparison of the PFS between the lung-irAE group (n = 36) and non-lung-irAE group (n = 120) was comparable (median 144 days, IQR: 73–401 days vs median 65 days, IQR: 39–177 days, $P = .262$) (A). Similarly, OS between lung-irAE group (n = 36) and non-lung-irAE group (n = 120) was not statistically significant (median 667 days, IQR: 305–1064 days vs median 458 days, IQR: 224–903 days, $P = .302$) (B).

not statistically significant (median 144 days, IQR: 73–401 days vs median 65 days, IQR: 39–177 days, $P = .262$) (Fig. 5A). Similarly, the OS between the lung-irAE group (n = 36) and non-lung-irAE group (n = 120) was comparable (median 667 days, IQR: 305–1064 days vs median 458 days, IQR: 224–903 days, $P = .302$) (Fig. 5B).

3.4.2. Overall survival in all irAE patients with or without lung-irAE after initiation of ICI treatment. Using the Kaplan–Meier method, among irAE patients (n = 82), PFS in lung-irAE (n = 36) and non-irAE (n = 46) patients was not statistically significant (median 144 days, IQR: 73–401 days vs median 96 days, IQR: 57–214 days, $P = .543$). Similarly, the OS of patients with (n = 36) or without lung-irAE (n = 46) was comparable (median 667 days, IQR: 305–1064 days vs median 425 days, IQR: 255–1052 days, $P = .603$) (Fig. 6A), and OS according to grade classification in the lung-irAE group was not statistically significant (Fig. 6B). Interestingly, grade 2 lung-irAE patients (n = 22) seemed to have better survival than those in grade 1 (n = 10), but the difference was not statistically significant (median 204 days, IQR: 95–642 days vs median 29 days, IQR: 14–89 days, $P = .099$).

4. Discussion

This study clearly demonstrated that the preferred period of irAE after induction of the ICIs was significantly longer in lung-irAE than in other major organs (skin, digestive tract, endocrine

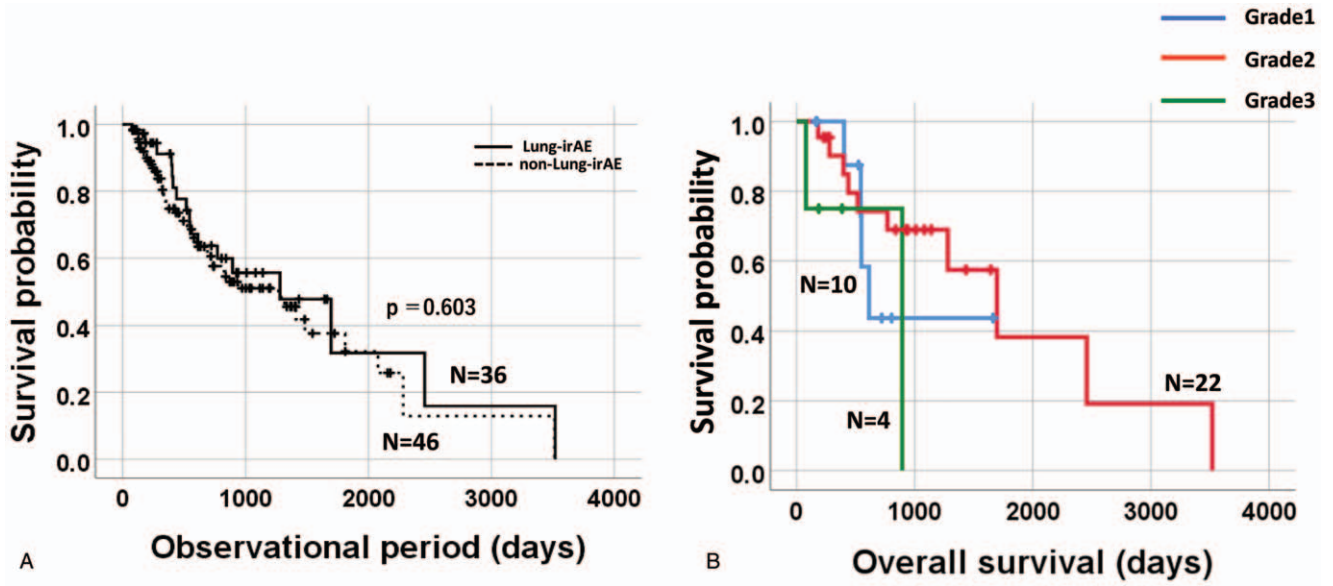

Figure 6. Overall survival among all 82 irAE patients showed lung-irAE (A) using the Kaplan–Meier method, among the irAE patients, OS with (n = 36) or without lung-irAE (n = 46) was comparable (median 667 days, IQR: 305–1064 days vs median 425 days, IQR: 255–1052 days, $P = .603$) (A), and that according to the grade classification in the lung-irAE group was not statistically significant (B). Grade 2 lung-irAE patients (n = 22) seemed to have a better survival than grade 1 patients (n = 10), but the difference was not statistically significant (median 204 days, IQR: 95–642 days vs median 29 days, IQR: 14–89 days, $P = .099$).

glands). Although irAE can lead to longer OS and PFS, as seen in recent studies,[2,3] it seemed not to be applicable to lung-irAE, even in consideration of the severity of lung toxicity.

IrAE usually occurs in the skin (10.5%), digestive tract (7.4%), endocrine glands (6.8%), and lungs (5.3%),[4] as seen in the present study. In general, irAE grade I–II events mainly affect the skin and the gut, whereas grade III–IV events are restricted mainly to the digestive tract. Furthermore, irAE leading to death was an extremely rare event with anti-PD-1 agents (pembrolizumab, 0.1%; nivolumab, 0.3%) and is most often secondary to pneumonitis.[5] In this regard, understanding the general aspect of lung-irAE is a critical issue for physicians.

To the best of our knowledge, few studies have described the time of onset of irAE after starting ICIs, which ranged from 8.9 weeks[6] to 10.8 weeks.[2] On the contrary, the present study revealed that lung-irAE occurred at a later phase (204 days after initiation of ICIs) and was significantly longer than non-lung-irAE (skin, endocrine, digestive tract) (median 29 days). This might be owing to a racial difference and/or predominant nivolumab use, approximately 80% of ICIs in this study.

Previous reports have described that irAEs can prolong OS and PFS by about 6 or 3 months, respectively.[7] This was confirmed by our results showing positive irAE effects, as in other studies.[2,8] Although nivolumab is well known to cause lung-irAE than cytotoxic T-lymphocyte antigen 4 (CTLA-4),[5] there are few reported data that describe the effects of lung-irAE on OS and PFS.[9] In this perspective, our study revealed that lung-irAE patients seemed to have a positive effect on the OS and PFS, but statistically not significant than in all enrolled patients. Interestingly, when we focused on the severity of pulmonary toxicity, grade 3 showed the worst prognosis, but the survival probability in grades 1 and 2 seemed to be better than in grade 3 without statistical significance. In contrast, Shen et al reported that treatment-related adverse events could predict the objective response rate (ORR) to immune checkpoint inhibitors.[10] Furthermore, the ORR had a positive coefficient correlation with the severity of treatment-related adverse events in non-small cell lung cancer.[10] Thus, we speculated that treatment response differed between irAE and non-irAE patients regardless of the type of lung cancer (i.e., adenocarcinoma or squamous carcinoma) or the number of involved organs, which led to a positive effect on PFS and OS via irAE.

Therefore, more indexed cases were required for further analysis to determine whether the severity of irAE has a positive effect on PFS and OS.

This study has a limitation in that it was retrospective. Our analysis was not performed by treatment regimen, pathological type, and the extent of PD-L1 expression in the tumor cells due to a relatively low number of lung-irAE patients. Furthermore, the enrolled patients received ICI at various times, but the proportion of ICI treatment as in the 1st or after 2nd regimens was comparable between the irAE and non-irAE groups. We did not examine PD-L1 expression or perform PD-L1 expression test on tumor cells for all enrolled patients, which led to the predominant use of nivolumab, but not pembrolizumab. However, the ratio of pembrolizumab use was equal in both groups. Altogether, our results reflect the real-world ICI treatment and/or the whole aspect of irAE.

We demonstrated the preferred timing of irAEs according to the major organs and specifically focused on the effect of irAEs on the lungs.

Studies in the future would require further index cases to confirm our findings.

5. Conclusion

Most irAEs occur in the skin, endocrine, digestive tract, and lung. Lung-irAE was recognized at a later phase and seemed not to prolong OS and PFS, even in consideration of the severity of lung toxicity, which was contrary to all irAEs in whole organs.

Author contributions

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Supervision: Saori Takata, Haruyuki Ishii, Hajime Takizawa.
Writing – original draft: Aya Hirata.
Writing – review & editing: Takeshi Saraya, Hajime Takizawa.

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