ORIGINAL ARTICLE

Clinical Impact of Pre-Existing Autoantibodies in Patients With SCLC Treated With Immune Checkpoint Inhibitor: A Multicenter Prospective Observational Study

Yuki Sato, MD,[a,*] Satoru Fujiwara, MD,[b] Akito Hata, MD,[c] Yoko Kida, MD,[d] Takahiro Masuda, MD,[d] Hisanori Amimoto, MD,[e] Hirotaka Matsumoto, MD,[f] Kotoko Miyoshi, MD,[g] Kojiro Otsuka, MD, PhD,[g] Keisuke Tomii, MD, PhD[a]

[a]Department of Respiratory Medicine, Kobe City Medical Center General Hospital, Kobe, Japan
[b]Department of Neurology, Kobe City Medical Center General Hospital, Kobe, Japan
[c]Department of Thoracic Oncology, Kobe Minimally Invasive Cancer Center, Kobe, Japan
[d]Department of Respiratory Medicine, Kobe City Nishi-Kobe Medical Center, Kobe, Japan
[e]Department of Respiratory Medicine, Kobe City Medical Center West Hospital, Kobe, Japan
[f]Department of Respiratory Medicine, Hyogo Prefectural Amagasaki General Medical Center, Amagasaki, Japan
[g]Department of Respiratory Medicine, Shinko Hospital, Kobe, Japan

Received 6 August 2023; revised 15 October 2023; accepted 15 November 2023
Available online - 19 November 2023

ABSTRACT

Introduction: Although pretreatment autoantibodies have been associated with immune-related adverse events (irAEs) and immune checkpoint inhibitor treatment efficacy in some types of cancer, their importance has not been evaluated in patients with SCLC.

Methods: A multicenter prospective observational study was conducted on a total of 52 patients with extensive-disease SCLC who received immune checkpoint inhibitors in combination with chemotherapy as the first-line treatment at either of the six participating centers in Japan. Pretreatment serum samples were collected and analyzed for autoantibodies (rheumatoid factor, antinuclear antibodies, and antithyroid). Moreover, 12 antineuronal antibodies (AMPH, CV2, PNMA2, Ri, Yo, Hu, Recoverin, SOX1, Titin, Zic4, GAD65, and Tr) were analyzed using immunoblot assays. The primary end point was the incidence of irAEs with or without autoantibodies. The secondary end points were progression-free survival (PFS) and overall survival (OS) on the basis of the presence or absence of autoantibodies.

*Corresponding author.

Disclosure: Dr. Sato received fees as a member of the speakers' bureau from AstraZeneca, Chugai Pharmaceutical, Merck Sharp & Dohme, Ono Pharmaceutical, Novartis, Pfizer, Taiho Pharmaceutical, Nippon Kayaku, Bristol Myers Squibb, Eli Lilly, Takeda, and Kyowa Kirin outside of the submitted work. Dr. Fujiwara received fees as a member of the speakers' bureau from Biogen Japan and Daiichi Sankyo outside of the submitted work. Dr. Hata received fees as a member of the speakers' bureau from Boehringer Ingelheim, Lilly, Chugai Pharma, AstraZeneca, and Pfizer, and received research funding from Boehringer Ingelheim, Merck Sharp & Dohme, Lilly, and AstraZeneca outside of the submitted work. Dr. Kida received fees as a member of the speakers' bureau from AstraZeneca, Ono Pharmaceutical, and Eli Lilly outside of the submitted work. Dr. Amimoto received fees as a member of the speakers' bureau from AstraZeneca, Chugai Pharmaceutical, Ono Pharmaceutical, and Taiho Pharmaceutical outside of the submitted work. Dr. Matsumoto received fees as a member of the speakers' bureau from Chugai Pharmaceutical, AstraZeneca, Eli Lilly, Taiho Pharmaceutical, Ono Pharmaceutical, Boehringer Ingelheim, Merck Sharp & Dohme, Takeda, and Nippon Kayaku outside of the submitted work. Dr. Otsuka received fees as a member of the speakers' bureau from AstraZeneca, Chugai Pharmaceutical, Merck Sharp & Dohme, Ono Pharmaceutical, Novartis, Pfizer, Eli Lilly, Takeda, Kyorin, Boehringer Ingelheim, Meiji Seika, GlaxoSmithKline, Taiho Pharmaceutical, Sanofi, and Nihon Shinyaku outside of the submitted work. Dr. Tomii received fees as a member of the speakers' bureau from Astellas, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Chugai Pharma, Daiichi Sankyo, Eli Lilly, GlaxoSmithKline, Kyorin, Kyowa Hakko Kirin, Merck Sharp & Dohme, Nippon Kayaku, Novartis Pharma, Pfizer, Sanofi, Shionogi, Taiho Pharmaceutical, and Teijin Pharma; and had an advisory role at Eli Lilly outside of the submitted work. The remaining authors declare no conflicts of interest.

Address for correspondence: Yuki Sato, MD, Department of Respiratory Medicine, Kobe City Medical Center General Hospital, 2-1-1 Minatojima-minamimachi, Chuo-ku, 650-0047, Kobe, Japan. E-mail: yuki1130sato@gmail.com

Cite this article as: Sato Y, Fujiwara S, Hata A, et al. Clinical impact of pre-existing autoantibodies in patients with SCLC treated with immune checkpoint inhibitor: a multicenter prospective observational study. *JTO Clin Res Rep*. 2023;4:100608.

ISSN: 2666-3643

https://doi.org/10.1016/j.jtocrr.2023.100608

Results: PFS and OS were 4.4 and 25.3 months, respectively. Autoantibodies (rheumatoid factor, antinuclear antibodies, and antithyroid antibodies) were detected in 29 patients (56%). In total, irAEs were observed in 18 patients (35%); irAE incidence was 48% in the autoantibody-positive group and 17% in the autoantibody-negative group ($p = 0.039$). There was no difference in PFS or OS between patients with and without autoantibodies (4.4 mo versus 4.6 mo, $p = 0.36$; 15.3 mo versus 18.2 mo, $p = 0.36$). Antineuronal antibodies were detected in 16 patients (31%). However, the development of neurologic irAEs was not observed in both groups.

Conclusions: Vigilance is required against the development of irAEs in pretreatment antibody-positive patients.

Keywords: Small-cell lung cancer; Immune-related adverse event; Autoantibody; Paraneoplastic autoantibody; Paraneoplastic neurologic syndrome

Introduction

SCLC accounts for 15% to 20% of lung cancer cases, and extensive-disease SCLC (ED-SCLC) accounts for approximately two-thirds of total SCLC cases.[1] Development of immune checkpoint inhibitors (ICIs) that target programmed death-ligand 1 (PD-L1) has markedly changed the treatment strategy for ED-SCLC, as reported in pivotal phase 3 trials.[2,3]

ICIs manifest inflammatory adverse effects, also known as immune-related adverse events (irAEs), which differ from those of conventional cytotoxic chemotherapy. Therefore, irAEs have attracted considerable clinical interest. In previous studies, the presence of pretreatment autoantibodies such as antinuclear antibodies (ANAs) and antithyroid antibodies was investigated for predicting the occurrence of irAEs and treatment efficacy of ICI in patients with NSCLC.[4,5] In another melanoma phase 3 combined cohort, baseline autoantibody signatures could predict the recurrence and toxicity of immunotherapy.[6] More specifically, anti-GNAL and anti-ITM2B autoantibodies were found associated with hypophysitis, whereas anti-CD74 autoantibodies were associated with pneumonitis.[7] In SCLC, a previous study reported that positivity for the autoimmune profile at baseline was associated with improved outcomes and severe ipilimumab toxicity.[8] However, the importance of autoantibodies has not been evaluated in patients with SCLC treated with chemotherapy and PD-L1 inhibitors.

Another important aspect of SCLC is the development of paraneoplastic neurologic syndrome (PNS) caused by SCLC tumor cells. PNS is a clinical complication frequently observed in patients with SCLC.[9] PNS results from the indirect effect of a tumor on the nervous system, without local invasion, or metastasis. Tumor cells are immunogenic and lead to the activation of both cell-mediated and humoral immune systems. Cytotoxic T cells recognize antigens on tumor cells and attack or generate antibodies against the tumor cells. However, the body's immune system can attack normal tissue with a similar antigen presentation, which leads to symptoms. Antineuronal antibodies play an important role in the pathogenesis of PNS, and the prevalence of antineuronal antibodies is 31% to 58% in patients with SCLC.[10,11] Theoretically, the use of ICIs may increase the risk of developing PNS by immune modulation, which has been exhibited in some mouse models.[12,13] Recently, a systematic review, and population-based study reported an increase in neurologic irAEs after the introduction of ICI therapy.[14,15] On the other hand, transcriptome analysis revealed that patients with ovarian cancer and SCLC with PNS harbored a high density of CD8+ lymphocytes.[16,17] Thus, ICI is a possible promising treatment strategy for patients with PNS. However, the safety and efficacy of administering ICI to patients with antineuronal antibodies is not well understood.[18]

In this multicenter prospective study, we aimed to investigate the clinical impact of preexisting autoantibodies, including antineuronal antibodies, on the occurrence of irAEs caused by first-line treatment with chemotherapy and ICI in patients with SCLC. Therefore, this study aimed to propose better management strategies for these patients.

Materials and Methods

Study Design and Patients

We prospectively enrolled patients with histologically or cytologically confirmed ED-SCLC, as defined according to the Veterans Administration Lung Study Group staging system,[19] who received platinum and etoposide with atezolizumab or durvalumab as the first-line treatment at either of the six participating hospitals in Japan between August 2019 and January 2022. The patients received ICI until the occurrence of unacceptable toxic effects or disease progression. This study was approved by the Kobe City Medical Center General Hospital Ethics Committee (zn190923) and conducted in accordance with the 1964 Declaration of Helsinki and its later amendments. All patients provided written informed consent before the start of the study. The study was registered in the University Medical Information Network Clinical Trials Registry (UMIN 000042962).

All patients were classified on the basis of their clinical stage according to the eighth edition of the TNM classification. Patients above 75 years of age were defined as older patients and poor performance status (PS) was defined by the Eastern Cooperative Oncology Group PS score of greater than or equal to 2. Smoking status was categorized as never (never smoked), current (smoked within 1 y of diagnosis), or former (other smoking status). Antitumor responses were assessed according to the Response Evaluation Criteria for Solid Tumors (version 1.1). Progression-free survival (PFS) was calculated as the interval between the date of commencement of combination therapy and the date of disease progression or death by any cause, whereas overall survival (OS) was calculated as the date of death by any cause. The attending physician evaluated AEs according to the Common Terminology Criteria for Adverse Events version 5.0.[20] Safety was investigated using AE data related to combination therapy. In a clinical context, AEs related to immunotherapy have been documented as irAEs. Severe irAEs were defined as grade 3 or higher.

Neurologic irAEs were defined as neurologic complications confirmed by laboratory, imaging, or other examinations, and considered to be linked to ICI by the treating physicians (oncologists and neurologists) and central review. Differential diagnoses such as infections or tumor infiltration were thoroughly ruled out. PNS classification on the basis of the 2021 criteria was used to diagnose irAEs. Chest-abdominal computed tomography and brain imaging studies were recommended every 6 to 9 weeks to evaluate treatment efficacy. The data cutoff date for the current analysis was September 30, 2022.

Autoantibody Analysis

Serum samples were collected before initiating the anticancer treatment and evaluated for the presence of autoantibodies (rheumatoid factor [RF], ANA, and antithyroid antibodies) in a blinded manner. We adopted a cutoff value of 15 IU/mL for RF and 1:40 for ANA, as previously reported.[4] According to this previous report that investigated pretreatment with autoantibodies, we defined patients with RF, ANA, or antithyroid antibodies as antibody-positive. Furthermore, commercial immunoblotting was used for detecting 12 antineuronal antibodies (AMPH, CV2/CRMP5, Ma2/PNMA2, Ri/ANNA-2, Yo/PCA-1, Hu/ANNA-1, Recoverin, SOX1, Titin, Zic4, GAD65, and Tr/DNER) (EUROLINE PNS 12 Ag [Euroimmun, Lubeck, Germany]).[21] Serum samples were analyzed according to the manufacturer's instructions. Specifically, immunoblot assays were performed on the EUROBlotOne system (Euroimmun), and bands were scanned and analyzed using EUROLineScan (Euroimmun), giving an arbitrary unit of intensity. According to the manufacturer's instructions, samples were considered negative when they presented an intensity between 0 and 5, weakly positive between 6, and 10, positive between 11 and 50 (11–25, +; 26–50, ++), and strongly positive (+++) at an intensity equal to or above 51. Cases with positive or strong positive bands were defined as antineuronal antibodies positive. In addition, ANA, and antithyroid antibodies were evaluated according to the instructions provided in package inserts.

Statistical Analysis

The prespecified primary end point was the incidence of irAEs according to the presence of autoantibodies. According to a previous report, the incidence of preexisting autoantibodies was 58%, and the incidence of irAEs was 73% with autoantibodies and 45% without autoantibodies.[4] Under this assumption, the required sample size to test the difference was 52 ($\alpha = 0.05$, two-sided, and $1\text{-}\beta = 0.70$). To allow protocol deviation, we planned the total number of patients to be 54. The key secondary end points were the presence of paraneoplastic autoantibodies and antineuronal antibodies, and the development of neurologic irAEs, PFS, and OS.

Continuous variables were expressed as median and interquartile range and compared using the Student's t test. Categorical variables were presented as numbers and percentages and compared using the chi-square test or Fisher's exact test. The Kaplan-Meier method was used to estimate survival outcomes, and groups were compared using the log-rank test and Cox proportional hazards model. Results were expressed as hazard ratio with a 95% confidence interval (CI). Statistical significance was defined as a two-sided p value of less than 0.05. Statistical analyses were conducted using JMP 16 software (SAS Institute, Cary, NC).

Results

Patient Characteristics and Overall Treatment Efficacy

Of the total participating patients, two were excluded from this study (one patient did not meet the inclusion criteria, and one patient underwent inappropriate blood sampling). Finally, this study included 52 patients with histologically confirmed SCLC; pretreatment baseline blood samples were used for serologic analysis (Supplementary Fig. 1). Patient characteristics are summarized in Table 1. The median age was 72.5 years (interquartile range: 67.25–76 y), and 41 patients (78.9%) were men. In this study, no patients had active

Table 1. Patient Characteristics

Characteristics	All Patients (N = 52)
Age (y), n (%)	
<75	31 (59.6)
≥75	21 (40.4)
Median (IQR)	72.5 (67.25-76)
Sex, n (%)	
Male	41 (78.9)
Female	11 (21.1)
ECOG PS, n (%)	
0	14 (26.9)
1	34 (65.4)
2	2 (3.8)
3	2 (3.8)
Smoking status, n (%)	
Never	3 (5.8)
Current or former	49 (94.2)
Histology, n (%)	
Small cell carcinoma	51 (98.1)
LCNEC	1 (1.9)
Previous treatment for SCLC, n (%)	
Chemoradiotherapy	10 (19.2)
Operation	3 (5.8)
Treatment naive	41 (78.8)
Treatment regimen, n (%)	
Platinum + etoposide +atezolizumab	39 (75.0)
Platinum + etoposide + durvalumab	13 (25.0)
Brain metastasis, n (%)	
Present	20 (38.5)
Absent	32 (61.5)
History of preexisting autoimmune disease	
Present	5 (9.6)
Absent	47 (90.0)

IQR, interquartile range; ECOG PS, Eastern Cooperative Oncology Group Performance Status; LCNEC, large cell neuroendocrine carcinoma.

symptoms of autoimmune disease, but some had a history of autoimmune disease. Specifically, two patients had rheumatoid arthritis, one had interstitial pneumonia, one had sarcoidosis, and one had membranous nephropathy. However, they did not receive particular treatment at the start of the study. The median PFS and OS were 4.4 (95% CI: 3.8–5.4) and 25.3 (95% CI: 9.9–not reached) months, respectively (Fig. 1*A* and *B*). The objective response rate (ORR) to chemoimmunotherapy was 69%, and the disease control rate was 86% (Supplementary Table 1). The median follow-up time from the commencement of chemoimmunotherapy was 10.5 months.

Evaluation of Preexisting Autoantibody Profile

Baseline serum sample results are summarized in Table 2. A total of 29 patients (56%) had at least one autoantibody at baseline. Among them, RF, ANA, and antithyroid were present in seven, 18, and seven patients (13%, 35%, and 13%), respectively. Moreover, antineuronal antibodies, predominantly SOX1, Hu, and Zic4 (13%, 10%, and 8%, respectively), were detected in 16 patients (31%).

Incidence of Autoantibodies Associated With IrAEs

The incidence of irAEs is summarized in Table 3. A total of 18 patients (35%) presented irAEs (any grade), and three patients (6%) had severe irAEs. Multiple irAEs were observed in six patients. Higher incidences of irAEs were observed in patients with autoantibodies than in patients without autoantibodies (48% in the autoantibody-positive group versus 17% in the autoantibody-negative group, $p = 0.039$). The incidence of severe irAEs did not significantly change but seemed to be more common in antibody-positive patients (10% versus 4%, $p = 0.40$). No grade 5 irAEs associated with the treatment regimen were observed in this study. The association of specific antibodies to irAE incidence was summarized in Supplementary Table 1. Among them, the preexisting RF, and antithyroid antibody were related to the occurrence of arthritis and thyroid dysfunction, respectively ($p = 0.04$, $p = 0.01$). After the commencement of chemoimmunotherapy, two patients with a history of rheumatoid arthritis were diagnosed with the exacerbation of preexisting autoimmune disease. Regarding ANA titer and irAEs, we conducted additional analyses but did not identify particular differences according to ANA titer levels. The corresponding data is shown in Supplementary Figure 2*A* and *B*. More importantly, no neurologic irAEs were observed in this cohort.

Impact of Autoantibodies on PFS, OS, and ORR

To investigate the impact of autoantibodies, the Kaplan-Meier curves of PFS and OS on the basis of the presence or absence of autoantibodies are illustrated in Figure 2*A* and *B*. Patients with or without autoantibodies exhibited similar PFS and OS (4.4 versus 4.6 mo, $p = 0.36$, and 15.3 versus 18.2 mo, $p = 0.36$, respectively). We also evaluated ORR and disease control rate, which exhibited no significant differences between the two groups (61% versus 78% and 79% versus 91%, respectively) (Supplementary Table 2).

Analysis of PFS and OS by Patient Characteristics

The PFS and OS according to the presence of irAE were illustrated in Figure 3*A* and *B*. Longer PFS and OS were observed in patients with irAE compared with patients without irAE (6.2 versus 3.9 mo, $p = 0.003$; 25.1 versus 13.0 mo, $p = 0.02$, respectively). Next, we conducted a subgroup analysis of PFS and OS on the basis of patient characteristics. The results are

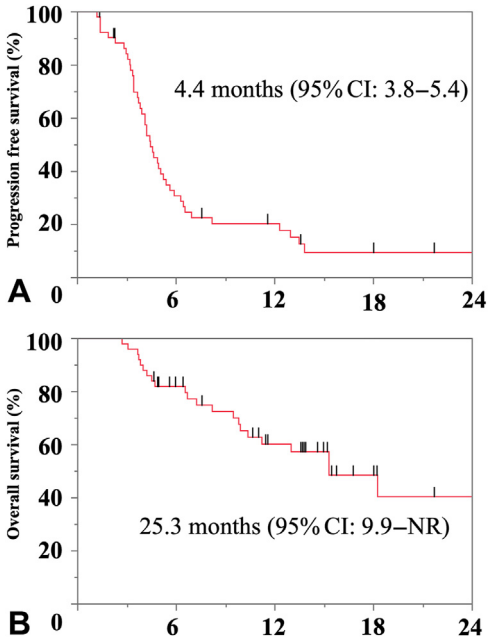

Figure 1. Kaplan-Meier progression-free survival (*A*) and overall survival (*B*) in overall patients. CI, confidence interval; NR, not reached.

presented in Supplementary Tables 3 and 4. Poor PS was a poor predictor of PFS and OS ($p = 0.02$ and <0.0001, respectively). The presence of autoimmune antibodies did not predict PFS or OS in multivariate analysis.

Table 2. Preexisting Autoimmune Antibody Profiles

Antibody	All Patients (N = 52)
Preexisting autoimmune antibody, n (%)	
Present	29 (56)
RF	7 (13)
ANA	18 (35)
Antithyroid	7 (13)
Absent	23 (44)
Preexisting antineuronal antibodies, n (%)	
Present	16 (31)
SOX1	7 (13)
Hu	5 (10)
Zic4	4 (8)
AMPH	2 (4)
Recoverin	2 (4)
PNMA2	1 (2)
Ri	1 (2)
Yo	1 (2)
CV2	0 (0)
Titin	0 (0)
GAD65	0 (0)
Tr	0 (0)
Absent	36 (69)

RF, rheumatoid factor; ANA, antinuclear antibody.

Discussion

To the best of our knowledge, this is the first prospective study to evaluate irAEs induced by chemotherapy and PD-L1 inhibitors, and their clinical impact in the first-line treatment of SCLC. Most importantly, we prospectively evaluated the occurrence of irAEs using pretreatment serum analysis for autoantibodies.

Firstly, our results reveal that baseline autoimmune antibodies predict the occurrence of irAEs, which may be useful in routine clinical settings. The prevalence of autoimmune antibodies and incidence of irAEs were comparable to those reported previously.[2–4] On the basis of our findings, vigilance is required against the development of irAEs in antibody-positive patients. Regarding irAE type, thyroid dysfunction, and arthritis were correlated with the baseline profile of autoantibodies (RF and antithyroid antibody). According to previous reports, thyroid autoimmunity may be involved in the development of thyroid irAEs.[22,23] In this study, patients with irAE exhibited longer PFS and OS compared with patients without irAE, which is concordant with the previous literature.[4] Despite the higher incidence of irAEs, treatment efficacy (defined by ORR, PFS, and OS) with or without autoantibodies did not differ, and the presence of preexisting autoantibodies did not affect PFS and OS. Previous reports on the prognostic impact of preexisting autoantibodies are highly controversial.[4,5] It is important to note that SCLC differs from NSCLC immunogenetically. Thus, further studies are warranted to determine the importance of autoantibodies in ICI treatment.

Another important finding of our study was the prevalence and clinical impact of antineuronal antibodies, which was 31% in our cohort. A previous study revealed anti-Hu as the most common antibody, consistent with our findings.[24] More importantly, neurologic irAEs were not observed in antineuronal antibody-positive or antibody-negative patients. In previous reports and clinical trials, the prevalence of neurologic irAEs was reported to be 0.5% to 1.22%, which is concordant with our analysis.[2,25] Clinically, we may not need to be concerned about developing neurologic irAE even in patients positive for antineuronal antibodies, but we should be cautious against routine evaluation of antineuronal antibodies before ICI initiation in patients without neurologic symptoms. In this study, the presence of preexisting antineuronal antibodies did not affect the treatment efficacy. Previous studies have reported controversial conclusions; one report suggested that anti-Hu antibodies were associated with better OS,[26] whereas another suggested that ORR was poor in patients with PNS.[27] These studies included various subtypes other than lung cancer; therefore, these differences should be validated separately.

A possible explanation for the lower diagnostic value of antineuronal antibodies in developing neurologic irAEs

Table 3. Summary of The Immune-Related Adverse Events

Immune-Related Adverse Events	All Grade	Grade ≥3	Autoantibody-Positive Patients (n = 29)	Autoantibody-Negative Patients (n = 23)	p[a]
Present, n (%)	18 (35)	4 (8)	14 (48)	4 (17)	0.039
Rash	5 (10)	0 (0)	4 (14)	1 (4)	0.37
Thyroid dysfunction	5 (10)	0 (0)	5 (17)	0 (0)	0.059
Pneumonitis	3 (6)	1 (2)	2 (7)	1 (4)	1.00
Arthritis	3 (6)	1 (2)	2 (7)	0 (0)	0.49
Colitis	3 (6)	0 (0)	2 (7)	1 (4)	1.00
Hepatitis (laboratory abnormalities)	1 (2)	1 (2)	0 (0)	1 (4)	0.44
Myositis	1 (2)	1 (2)	1 (3)	0 (0)	1.00
Nephritis (laboratory abnormalities)	1 (2)	0 (0)	0 (0)	1 (4)	0.44
Vasculitis	1 (2)	0 (0)	1 (3)	0 (0)	1.00
Stomatitis	1 (2)	0 (0)	1 (3)	0 (0)	1.00
Exacerbation of preexisting autoimmune disease	2 (4)	1 (2)	2 (7)	0 (0)	0.49

[a]*p* value is the comparison between autoantibody-positive and negative patients.

could be the diagnostic quality of immunoblot assays. Previously, a higher false-positive rate of immunoblot assays has been reported.[28–31] Our analysis suggests that a positive test for any antineuronal antibody should be addressed according to the clinical setting or confirmed by other methods.[32] In this study, we adopted this assay because this is readily available in Japan and covers sufficient antibodies for the PNS diagnosis of SCLC. Physicians must acknowledge that the diagnosis of PNS should always be performed in collaboration with neurologists. According to the current guidelines for the diagnosis of PNS, antineuronal antibody positivity, and relevant neurologic symptoms are needed.[33] Therefore, in clinical practice, we should take care to minimize false-positive antibody results, so that the overdiagnosis of PNS does not occur.

The limitation of our study includes a small sample size. Moreover, we were unable to analyze all antineuronal antibodies, such as surface antibodies (namely voltage-gated calcium channels or N-methyl-D-aspartic acid, etc.). In addition, no longitudinal serum sampling was conducted in this analysis. The evolution of the appearance of autoimmune antibodies could be informative for predicting the occurrence of irAE. As to the nature of this multicentered study, the judgment of irAE might differ from institution or clinicians. In addition, it may affect when determining the grading of irAE. However, the institutes that participated in this study were high-volume centers, and the physicians were well-experienced with lung cancer treatment. Therefore, we speculate that these concerns were minimized in this prospective study. In addition, the results of typically used antibodies, such as ANA, which were analyzed outside of this study might influence clinical judgment.

In conclusion, we evaluated the presence of autoimmune antibodies that may predict the development of irAEs. Furthermore, 31% of patients with SCLC were positive for antineuronal antibodies, as evaluated by immunoblot assay. In addition, the presence of antineuronal antibodies did not increase the risk of developing neurologic irAEs. However, further research is required to fully understand the role of autoantibodies in ICI treatment.

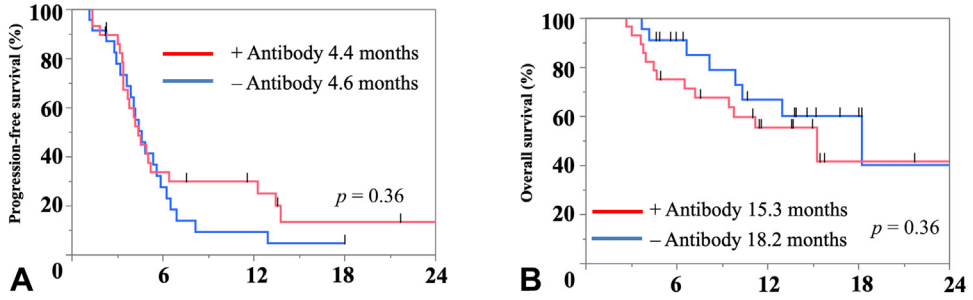

Figure 2. Kaplan-Meier progression-free survival (*A*) and overall survival (*B*), according to the presence of autoantibodies.

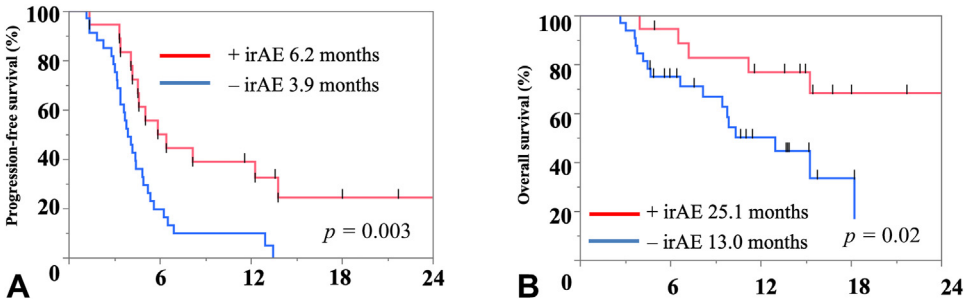

Figure 3. Kaplan-Meier progression-free survival (*A*) and overall survival (*B*), according to the presence of irAE. irAE, immune-related adverse events.

CRediT Authorship Contribution Statement

Yuki Sato: Data curation, Methodology, Formal analysis, Funding acquisition, Investigation, Resources, Visualization, Project administration, Writing - original draft, Writing - review & editing.

Satoru Fujiwara: Investigation, Validation, Writing - original draft, Writing - review & editing.

Akito Hata: Investigation, Resources, Writing - original draft, Writing - review & editing.

Yoko Kida: Investigation, Resources, Writing - review & editing.

Takahiro Masuda: Investigation, Resources, Writing - review & editing.

Hisanori Amimoto: Investigation, Resources, Writing - review & editing.

Kotoko Miyoshi: Investigation, Resources, Writing - review & editing.

Kojiro Otsuka: Investigation, Resources, Writing - review & editing.

Keisuke Tomii: Conceptualization, Methodology, Project administration, Funding acquisition, Supervision, Writing - original draft, Writing - review & editing.

Acknowledgments

This study was supported by internal funding from Kobe City Medical Center General Hospital and Kasahara Cancer Research Funding, Kobe, Japan. The authors thank Keiko Sakuragawa, Kanako Masuta, and Misa Aoyama for their administrative assistance. The authors also thank Editage (www.editage.com) for the English language editing.

Data Access

The corresponding author declares that he had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Data Sharing Statement

The data used in this article will be shared on reasonable request from the corresponding authors.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at https://doi.org/10.1016/j.jtocrr.2023.100608.

References

1. Wang S, Tang J, Sun T, et al. Survival changes in patients with small cell lung cancer and disparities between different sexes, socioeconomic statuses and ages. *Sci Rep*. 2017;7:1339.
2. Horn L, Mansfield AS, Szczęsna A, et al. First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. *N Engl J Med*. 2018;379:2220-2229.
3. Paz-Ares L, Dvorkin M, Chen Y, et al. Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. *Lancet*. 2019;394:1929-1939.
4. Toi Y, Sugawara S, Sugisaka J, et al. Profiling preexisting antibodies in patients treated with anti-PD-1 therapy for advanced non-small cell lung cancer. *JAMA Oncol*. 2019;5:376-383.
5. Yoneshima Y, Tanaka K, Shiraishi Y, et al. Safety and efficacy of PD-1 inhibitors in non-small cell lung cancer patients positive for antinuclear antibodies. *Lung Cancer*. 2019;130:5-9.
6. Johannet P, Liu W, Fenyo D, et al. Baseline serum autoantibody signatures predict recurrence and toxicity in melanoma patients receiving adjuvant immune checkpoint blockade. *Clin Cancer Res*. 2022;28:4121-4130.
7. Tahir SA, Gao J, Miura Y, et al. Autoimmune antibodies correlate with immune checkpoint therapy-induced toxicities. *Proc Natl Acad Sci U S A*. 2019;116:22246-22251.
8. Arriola E, Wheater M, Galea I, et al. Outcome and biomarker analysis from a multicenter phase 2 study of ipilimumab in combination with carboplatin and etoposide as first-line therapy for extensive-stage SCLC. *J Thorac Oncol*. 2016;11:1511-1521.
9. Graus F, Delattre JY, Antoine JC, et al. Recommended diagnostic criteria for paraneoplastic neurological syndromes. *J Neurol Neurosurg Psychiatry*. 2004;75:1135-1140.
10. Pittock SJ, Kryzer TJ, Lennon VA. Paraneoplastic antibodies coexist and predict cancer, not neurological syndrome. *Ann Neurol*. 2004;56:715-719.

11. Raspotnig M, Vedeler C, Storstein A. Paraneoplastic neurological syndromes in lung cancer patients with or without onconeural antibodies. *J Neurol Sci*. 2015;348:41–45.
12. Graus F, Dalmau J. Paraneoplastic neurological syndromes in the era of immune-checkpoint inhibitors. *Nat Rev Clin Oncol*. 2019;16:535–548.
13. Yshii LM, Gebauer CM, Pignolet B, et al. CTLA4 blockade elicits paraneoplastic neurological disease in a mouse model. *Brain*. 2016;139:2923–2934.
14. Marini A, Bernardini A, Gigli GL, et al. Neurologic adverse events of immune checkpoint inhibitors: a systematic review. *Neurology*. 2021;96:754–766.
15. Vogrig A, Fouret M, Joubert B, et al. Increased frequency of anti-Ma2 encephalitis associated with immune checkpoint inhibitors. *Neurol Neuroimmunol Neuroinflamm*. 2019;6:e604.
16. Vialatte de Pemille C, Berzero G, Small M, et al. Transcriptomic immune profiling of ovarian cancers in paraneoplastic cerebellar degeneration associated with anti-Yo antibodies. *Br J Cancer*. 2018;119:105–113.
17. Iams WT, Shiuan E, Meador CB, et al. Improved prognosis and increased tumor-infiltrating lymphocytes in patients who have SCLC with neurologic paraneoplastic syndromes. *J Thorac Oncol*. 2019;14:1970–1981.
18. Vogrig A, Muniz-Castrillo S, Joubert B, et al. Central nervous system complications associated with immune checkpoint inhibitors. *J Neurol Neurosurg Psychiatry*. 2020;91:772–778.
19. Micke P, Faldum A, Metz T, et al. Staging small cell lung cancer: veterans administration lung study group versus international association for the study of lung cancer-what limits limited disease? *Lung Cancer*. 2002;37:271–276.
20. National Cancer Institute. NCI guidelines for investigators: adverse event reporting requirements for DCTD (CTEP AND CIP) AND DCP INDs AND IDEs. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/aeguidelines.pdf. Accessed May 22, 2023.
21. Dechelotte B, Muniz-Castrillo S, Joubert B, et al. Diagnostic yield of commercial immunodots to diagnose paraneoplastic neurologic syndromes. *Neurol Neuroimmunol Neuroinflamm*. 2020;7:e701.
22. Kurimoto C, Inaba H, Ariyasu H, et al. Predictive and sensitive biomarkers for thyroid dysfunctions during treatment with immune-checkpoint inhibitors. *Cancer Sci*. 2020;111:1468–1477.
23. Kobayashi T, Iwama S, Yamagami A, et al. Elevated TSH level, TgAb, and prior use of ramucirumab or TKIs as risk factors for thyroid dysfunction in PD-L1 blockade. *J Clin Endocrinol Metab*. 2022;107:e4115.
24. Seluk L, Taliansky A, Yonath H, et al. A large screen for paraneoplastic neurological autoantibodies; diagnosis and predictive values. *Clin Immunol*. 2019;199:29–36.
25. Plaçais L, Michot JM, Champiat S, et al. Neurological complications induced by immune checkpoint inhibitors: a comprehensive descriptive case-series unravelling high risk of long-term sequelae. *Brain Commun*. 2021;3:fcab220.
26. de Jongste AH, van Gelder T, Bromberg JE, et al. A prospective open-label study of sirolimus for the treatment of anti-Hu associated paraneoplastic neurological syndromes. *Neuro Oncol*. 2015;17:145–150.
27. Oliveira V, Videira G, Samoes R, Carneiro P, Neves E, Santos E. Paraneoplastic neurological syndromes with onconeural antibodies: a single center retrospective study. *J Neurol Sci*. 2020;418:117103.
28. Abboud H, Rossman I, Mealy MA, et al. Neuronal autoantibodies: differentiating clinically relevant and clinically irrelevant results. *J Neurol*. 2017;264:2284–2292.
29. Budhram A, Nicolle MW, Yang L. The positive predictive value of onconeural antibody testing: a retrospective review. *Can J Neurol Sci*. 2018;45:577–579.
30. Vogrig A, Gigli GL, Segatti S, et al. Epidemiology of paraneoplastic neurological syndromes: a population-based study. *J Neurol*. 2020;267:26–35.
31. Ruiz-Garcia R, Martinez-Hernandez E, Saiz A, Dalmau J, Graus F. The diagnostic value of onconeural antibodies depends on how they are tested. *Front Immunol*. 2020;11:1482.
32. Graus F, Dalmau J. Paraneoplastic neurological syndromes. *Curr Opin Neurol*. 2012;25:795–801.
33. Graus F, Vogrig A, Muñiz-Castrillo S, et al. Updated diagnostic criteria for paraneoplastic neurologic syndromes. *Neurol Neuroimmunol Neuroinflamm*. 2021;8:e1014.