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Outcomes of Combined Atezolizumab Plus Chemotherapy in Non-small Cell Lung Cancer Patients in Clinical Practice

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Abstract. *Background/Aim: Atezolizumab, one of the anti-PD-L1 antibodies, targets PD-L1 expressed on cancer cells and antigen-presenting cells. This immune checkpoint inhibitor is now commonly used in combination with chemotherapy. The objectives of this study were to confirm the treatment outcomes of combined atezolizumab plus chemotherapy, and to identify prognostic factors, with a particular focus on the impact of the site of metastasis in real-world clinical practice. Patients and Methods: A retrospective review of clinical information on non-small cell lung cancer patients who received combined atezolizumab plus chemotherapy from May 2018 to August 2024 at our 11 hospitals was conducted. Results: The 141 patients evaluated had a median progression-free survival of 8.0 months and a median overall survival of 19.0 months. Multivariate analyses showed that 'absence of liver metastases', 'absence of adrenal metastases', 'first-line combined atezolizumab plus chemotherapy', and 'good performance status' were associated with progression-free survival and overall survival. Immune-related adverse events were observed in 27.7% of patients, with grade 3 or higher in 9.9% of patients, and grade 5 in 2.1% of patients. Conclusion: Efficacy and immune-related adverse events associated with the combination of atezolizumab and chemotherapy in non-small cell lung cancer patients were comparable to previous clinical trials. To ensure that appropriate patients receive the most effective treatment, it is important to identify detailed prognostic factors, including clinical information, such as the affected metastatic organs. Continued research and further accumulation of knowledge in this area are eagerly anticipated.*

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Key Words: Atezolizumab, chemotherapy, non-small cell lung cancer, clinical practice.

Immune checkpoint inhibitors (ICIs) have revolutionized the treatment of advanced non-small cell lung cancer (NSCLC). Among ICIs, anti-programmed death-1 (PD-1) and anti-programmed death ligand-1 (PD-L1) antibody drugs have been introduced into clinical practice. These drugs exert their anti-tumor effects by blocking the binding between PD-1 and PD-L1, which acts as a brake on the activity of T cells. By

inhibiting this pathway, the drugs reactivate T cells that have been suppressed by PD-L1, enhancing their ability to attack cancer cells. One of the anti-PD-L1 monoclonal antibodies, atezolizumab, binds to PD-L1 expressed on cancer cells and antigen-presenting cells, thereby inhibiting its interaction with PD-1 (1, 2). Like other ICIs, with favorable clinical trial results, atezolizumab has been used in clinical practice as a single agent. Thereafter, clinical trials in advanced NSCLC have demonstrated the efficacy of atezolizumab in combination with several cytotoxic antineoplastic agents (3-6). As a result, several treatment regimens – the IMpower150 regimen with paclitaxel combination (3), IMpower130 regimen with nab-paclitaxel combination (4), IMpower132 regimen with pemetrexed combination (5), and IMpower133 regimen with etoposide (6) – are now available in clinical practice. However, there have been no studies to date evaluating the treatment outcomes of combined atezolizumab plus chemotherapy in real-world clinical practice involving more than 100 patients, and the treatment outcomes obtained in clinical trials have not been sufficiently verified. In the treatment of advanced NSCLC, control of brain metastases is important for maintaining quality of life and has become a key area of focus (7). Besides brain metastasis, metastasis to the liver and adrenal glands are of note in relation to prognosis (8, 9). From this perspective, it is necessary to consider the organs of metastasis when analyzing factors related to prognosis in the treatment of NSCLC with ICIs. However, studies addressing this aspect have not been conducted.

In light of this, we conducted this retrospective study with the aim of clarifying the following two points: to evaluate the treatment outcomes of atezolizumab combined with chemotherapy in real-world clinical practice, and to identify prognostic factors with a particular focus on the site of metastasis. We believe that our results will provide useful information for optimizing future treatments involving this combination therapy.

Patients and Methods

Patients. This survey included all patients who received atezolizumab combined with chemotherapy at 11 medical institutions participating in the ATTENTION IBARAKI study group between May 2018 and August 2024. Medical records of eligible patients were reviewed in detail. However, patients who tested positive for driver genes and received a tyrosine kinase inhibitor targeting those genes as first-line treatment were excluded from the study. Pathological diagnosis was according to the World Health Organization classification (10). Imaging was performed at the time of diagnosis, and the clinical stage was determined according to the TNM classification (11). In addition to patient background information, such as age, sex, Eastern Cooperative Oncology Group performance status (PS), histology, and stage, we investigated the presence or absence of brain, liver, and adrenal metastases, and examined their relationship to prognosis. Tumor response was evaluated as complete response (CR), partial response (PR), stable disease, progressive disease, or not evaluable according to Response Evaluation Criteria in Solid Tumors (12). For each patient, progression-free survival (PFS) and overall survival (OS) from the start of atezolizumab plus chemotherapy were examined. Immune-related adverse events (irAEs) were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0), and adverse events were evaluated and graded accordingly (13).

Table I. *Patient characteristics*.

Number of patients	141
Sex, Female: Male	31:110
Performance status, 0-1:<2	116:25
Age, >70 years:70 years or older	70:71
Age, median (range), years	70 (38-87)
Pathology, adenocarcinoma:others	91:50
PD-L1, positive:negative	62:79
Stage, IIIA-C:IVA-B	17:124
Brain metastasis, absent:present	111:30
Liver metastasis, absent:present	121:20
Adrenal gland metastasis, absent:present	125:16

PD-L1: Programmed death ligand 1.

Statistical analysis. The chi-squared test was applied to test for differences in proportions. The Kruskal–Wallis test was used to compare values among four unpaired groups, such as when comparing patient age. Univariate analysis of survival probability was performed using the log-rank test and Kaplan–Meier method. Multivariate analysis was performed with the Cox proportional hazards model using significant factors identified in the univariate analysis. Logistic regression analysis was also performed to analyze long-term survival, although this study focused on three-year OS. In this study, a p-value less than 0.05 was considered to indicate a significant difference.

Informed consent and approval of Institutional Review Board. Comprehensive consent regarding lung cancer treatment was obtained from each patient. The ethical committees of the University of Tsukuba Mito Medical Center Mito Kyodo Hospital (NO-22-42-CHEMO) and participating institutions approved this study.

Results

Characteristics of patients. During the study period, 141 patients received he combination of atezolizumab and chemotherapy, and information on these patients was collected. Patient characteristics are shown in Table I. The median age of the cohort was 70 years (range=38-87 years). One hundred and ten (78.0%) were male patients. Ninety-one patients (64.5%) had adenocarcinoma. One hundred and sixteen patients (82.3%) had PS 0-1. Three patients (2.1%) tested positive for a driver gene mutation, all of whom had an epidermal growth factor receptor exon 20 insertion.

The treatment regimens administered and the number of patients treated were as follows: atezolizumab + bevacizumab + paclitaxel + carboplatin (IMpower150 regimen, paclitaxel

Table II. *Patient characteristics by atezolizumab treatment regimen.*

	Treatment regimen of Atezolizumab				
	PTX-containing	Nab-PTX-containing	PEM-containing	VP-containing	*p*-Value
	IMpower150	IMpower130	IMpower132	IMpower133	
Number of patients	80	22	14	25	
Sex, Female: Male	17:63	3:19	5: 9	6:19	0.472
Performance status, 0-1:<2	70: 10	17:5	12:2	17:8	0.140
Age, >70 years:70 years or older	43:37	8:14	8:6	11:14	0.436
Age, median (range), years	69 (48-81)	72 (38-98)	71 (45-79)	70 (47-84)	0.617
Pathology, adenocarcinoma:others	67:13	13:9	11:3	0:25	0.001
PD-L1, positive:negative	46:34	9:13	6:8	1:24	0.001
Stage, IIIA-C:IVA-B	6:74	4:18	3:11	4:21	0.276
Brain metastasis, absent:present	60:20	18:4	12:2	21:4	0.657
Liver metastasis, absent:present	74:6	20:2	13:1	14:11	0.001
Adrenal gland metastasis, absent:present	72:8	18:4	14:0	21:4	0.321

PD-L1: Programmed death ligand 1; PTX: paclitaxel; PEM: pemetrexed; VP: etoposide.

regimen) for 80 patients (56.7%); carboplatin + nab-paclitaxel + atezolizumab (IMpower130 regimen, nab-paclitaxel regimen) for 22 patients (15.6%); and platinum + pemetrexed + atezolizumab (IMpower132 regimen, pemetrexed regimen) for 14 patients (9.9%). In addition, 25 patients (17.7%) were treated with carboplatin + etoposide + atezolizumab (IMpower133 regimen, etoposide regimen) for large-cell neuroendocrine carcinoma. The characteristics of the patients receiving each particular regimen are shown in Table II.

In the 141 patients treated with atezolizumab plus chemotherapy, the response rate (CR + PR) was 56.0% (CR, n=3; PR, n=76). Forty-four patients (31.2%) were observed to have stable disease, with a disease control rate of 87.2%.

Survival analysis. During the study period, 79 of the 141 patients died. At data cutoff (August 31, 2024), the median patient follow-up time from initiation of combined atezolizumab plus chemotherapy to the date of death or data cutoff was 12.0 months (range=1.0-64.0 months). In the 141 patients, median PFS was 8.0 months [95% confidence interval (CI)=5.8-10.2 months; Figure 1A] and median OS was 19.0 months (95%CI=11.1-26.9 months; Figure 1B). The median PFS (Figure 2A-D) and OS (Figure 2E-H) for each regimen were as follows: for the paclitaxel regimen (IMpower150), median PFS was 7.0 months (95%CI=5.3-8.7 months) and median OS was 17.0 months (95%CI=4.1-30.0 months). For the nab-paclitaxel regimen (IMpower130), median PFS and OS were regarded as "not reached". For the pemetrexed regimen (IMpower132), the median PFS was 8.0 months (95%CI=4.4-11.6 months) and median OS was 19.0 months (95%CI=7.6-20.4 months). For the etoposide regimen (IMpower133), the median PFS was 7.0 months (95%CI=0.5-13.5 months) and median OS was 13.0 months (95%CI=6.0-20.0 months).

The treatment sequences of each regimen, including combined atezolizumab plus chemotherapy, therapies other than combined atezolizumab plus chemotherapy, and palliative care only, are shown in Figure 3. Seventeen of 141 patients (12.1%) had a period of palliative care alone without anticancer treatment lasting more than six months, with a median duration of nine months (range=6-51 months).

Factors that contribute to survival. With the aim to identify favorable factors influencing PFS and OS, univariate analysis was carried out with the following variables: sex, PS, age, PD-L1 expression, stage, pathology, brain metastasis, liver metastasis, adrenal gland metastasis, irAEs, atezolizumab-containing treatment line, and regimen of atezolizumab. For PFS, 'absence of liver metastasis', 'absence of adrenal gland metastasis', and 'first-line combined atezolizumab plus chemotherapy' were significantly associated with improved outcomes (Table III). 'No liver metastasis' and 'no adrenal gland metastasis' were significantly associated with OS (Table IV). Logistic regression analysis of three-year OS revealed that PS 0 was a favorable prognostic factor (Table V). In both analytic methods, neither the 'development of grade 2-4 irAE' not the 'absence or presence of brain metastases' was associated with OS.

Toxicity. IrAEs are shown in Table VI. Thirty-nine of the 141 patients (27.7%) had irAEs of any grade, and 14 (9.9%) had irAEs of grade 3 or higher. Thirty-two patients developed one irAE, six patients developed two irAEs, and one patient developed three irAEs. The majority of irAEs were manageable and reversible, but grade 5 irAEs occurred in three patients (2.1%), including two (1.4%) with grade 5 pulmonary irAEs. All three patients were male and aged

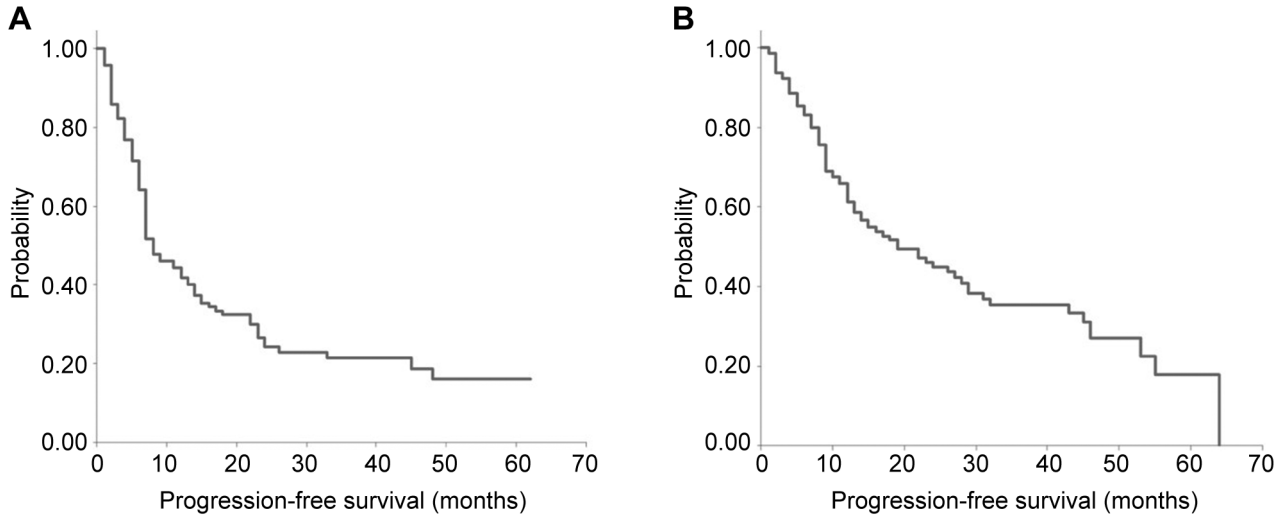

Figure 1. *In the 141 patients who were treated with atezolizumab plus chemotherapy, the median progression-free survival was 8.0 months [95% confidence interval (CI)=5.8-10.2 months] (A) and median overall survival was 19.0 months (95%CI=11.1-26.9 months) (B).*

between 69 and 79 years. The irAEs occurred 1-3 months after initiating combined atezolizumab plus chemotherapy. Both grade 5 pulmonary irAEs occurred in patients treated with the paclitaxel regimen, and grade 5 sepsis developed in a patient treated with the nab-paclitaxel regimen.

Discussion

Anti-PD-L1 antibodies, including atezolizumab, and anti-PD-1 antibodies have different binding sites, and this difference affects efficacy and safety (14). Clinical evaluations have shown that anti-PD-L1 antibodies have a lower incidence of irAEs and pneumonitis (15-17). At present, combined ICI plus chemotherapy or the combination of two ICIs has become the mainstream treatment for patients with driver gene-negative NSCLC. Among these treatments, there is insufficient information on the usefulness and irAEs of combined atezolizumab plus chemotherapy in clinical practice. Therefore, we conducted the present study to address this gap. In the 141 patients treated with the combination of atezolizumab and chemotherapy, the median PFS and OS was 8.0 months and 19.0 months, respectively. The respective median PFS and OS of the four regimens used were 7.0-8.0 months and 13.0-19.0 months.

In clinical trials of combined ICI plus chemotherapy, the median age was 63-64 years, and PS was almost limited to 0-1 (3-6). In patients with a favorable background suitable for clinical trials, the median PFS and OS were 7.0-8.3 months and 17.5-19.0 months, respectively (3-6, 18-21). In recent clinical trials examining combinations of two ICIs plus chemotherapy, median PFS and OS were 5.5-7.2 months and 13.3-17.1 months, respectively (20, 21). In various clinical trials, respective PFS and OS with atezolizumab in combination with chemotherapy were as follows: 8.3 and 19.0 months (3), 7.0 and 18.6 months (4), 7.6 and 17.5 months (5), and 5.2 and 12.3 months (6) for the paclitaxel, nab-paclitaxel, pemetrexed, and etoposide regimens, respectively. In contrast, in real-world clinical practice, PFS and OS for anti-PD-1 antibodies plus chemotherapy were 6.4-9.4 months and 15.9-21.8 months, respectively (8, 22, 23). To the best of our knowledge, there has been only one report by Ikeuchi *et al*. on the results of combined atezolizumab plus chemotherapy in clinical practice (24). In their report, the median age of 30 patients studied was 69 years, including 3.3% with PS 2, and 23.3% carried a mutation in the epidermal growth factor receptor gene (24). Their patients were treated with the paclitaxel regimen, and the median PFS was 8.3 months; however, OS was regarded as "not reached" (24). ICI-induced pneumonitis occurred in one patient (3.3%). In our 141 patients, the median age was 70 years, and included 17.4% with a PS of 2, and 2.8% were driver gene-positive. Despite the differences in patient background, the PFS and OS were similar to those of previous clinical trials, and we considered that the results of these trials were confirmed.

Although clinical trials have reported the proportion of patients with metastases, only a limited number of trials have specified the number of patients with brain, liver, or adrenal metastases (5, 25), which can influence patient outcomes. Meanwhile, in clinical practice, the frequency of these brain, liver, and adrenal metastases is reported to be around 10.4%-22.7%, 8.6%-15.0%, and 5.0%-13.0%, respectively (7-9). The proportion of these organ metastases in patients in this study was similar to those reported in previous studies (7-9),

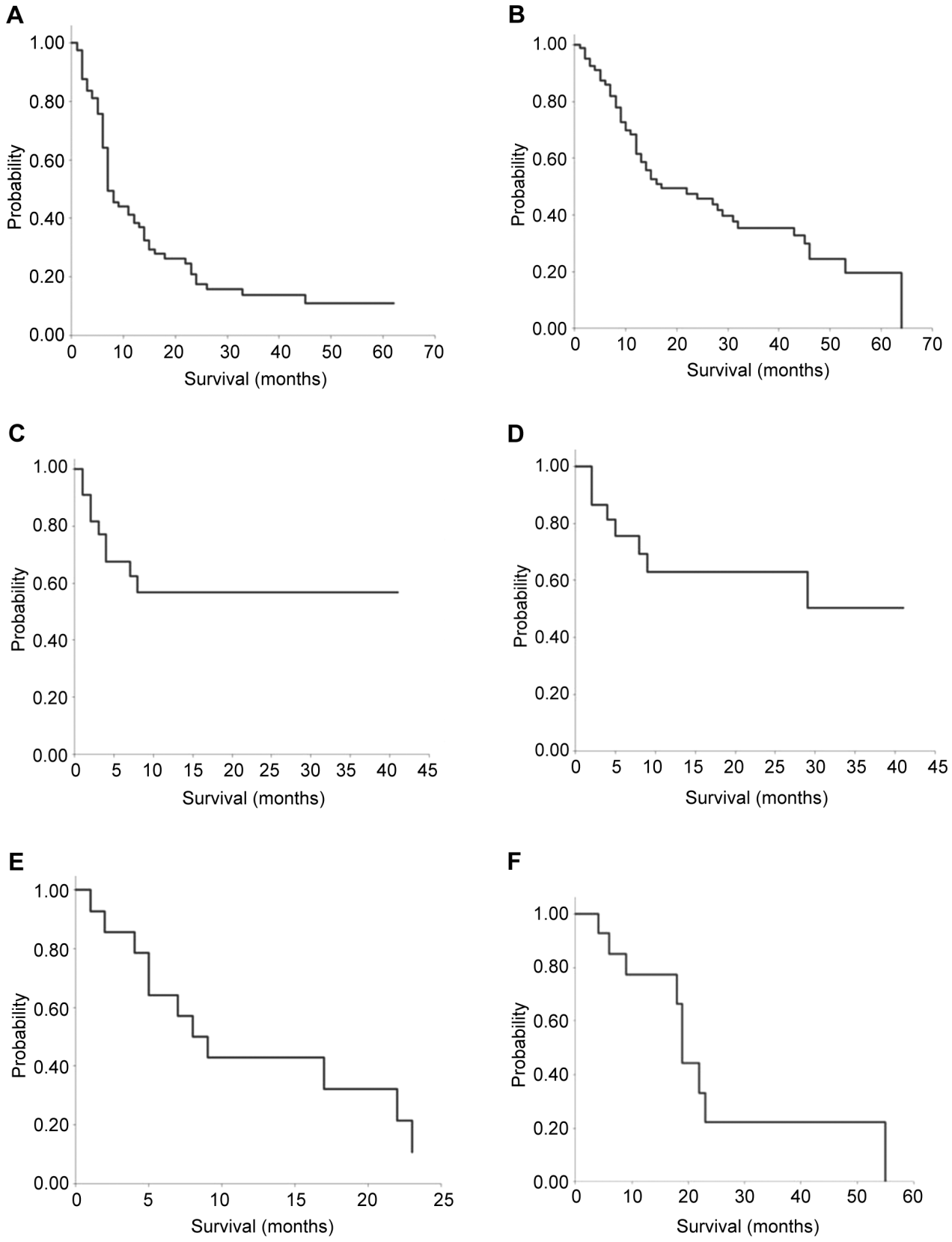

Figure 2. *Continued*

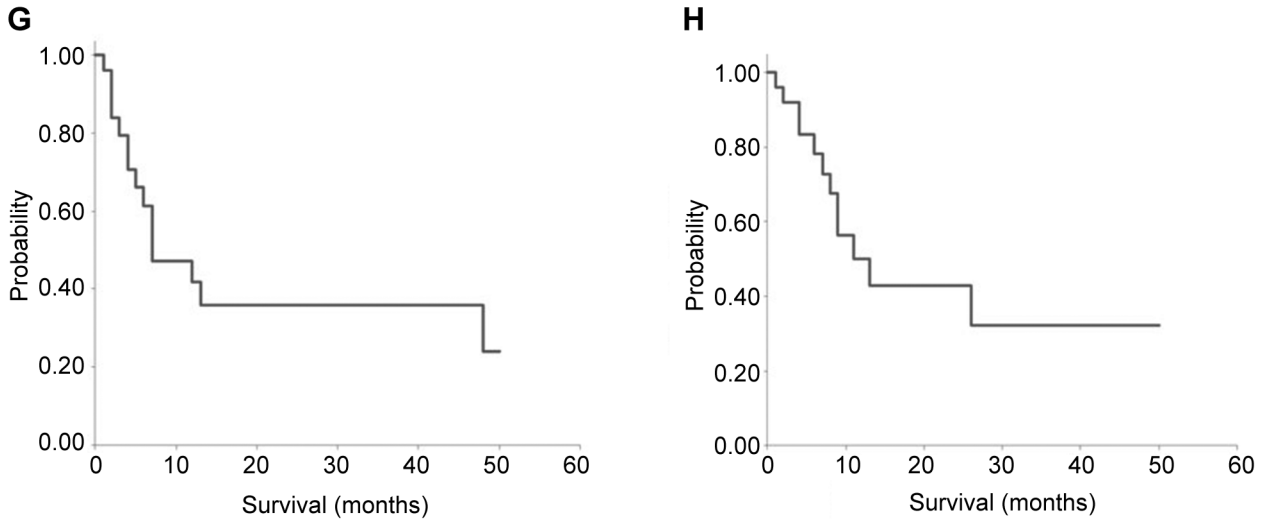

Figure 2. *Progression-free survival (PFS) and overall survival (OS) for each treatment regimen. The median PFS of the paclitaxel regimen (IMpower150) was 7.0 months (A), 'not reached' for the nab-paclitaxel regimen (IMpower130) (B), 8.0 months for the pemetrexed regimen (C), and 7.0 months for the etoposide regimen, (D). The median OS of the paclitaxel regimen (IMpower150) was 17.0 months (E), 'not reached' for the nab-paclitaxel regimen (IMpower130) (F), 19.0 months for the pemetrexed regimen (G), and 13.0 months for the etoposide regimen (H).*

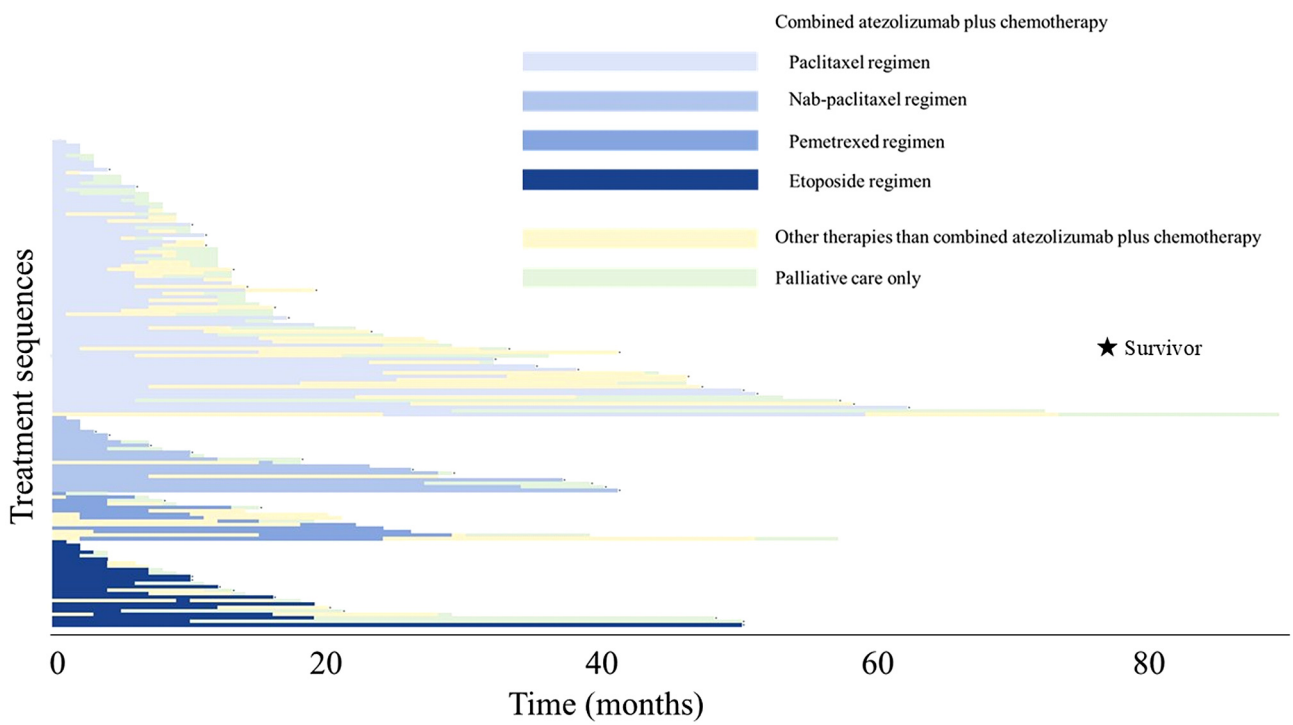

Figure 3. *The specific treatment sequences for the 141 patients with non-small cell lung cancer who were treated with combined atezolizumab plus chemotherapy.*

and this study represents treatment outcomes in patients that reflect clinical practice. This study, considering distant metastatic organs, showed that 'absence of liver metastasis', 'absence of adrenal metastasis', 'combined atezolizumab plus chemotherapy as first-line therapy', and 'good PS' might be related to prognosis. However, it is noteworthy that

Table III. *Uni- and multivariate analyses of favorable factors in progression-free survival.*

	Analysis			
	Univariate	Multivariate		
Factor	*p*-Value	*p*-Value	Hazard ratio	95%CI
Sex: Female	0.561			
PS: 0	0.033	0.116	1.641	0.885-3.043
Age: less than 70 years	0.291			
PD-L1: positive	0.319			
Pathology: Adenocarcinoma	0.234			
Stage: IIIA-C	0.390			
Brain metastasis: none	0.527			
Liver metastasis: none	0.001	0.001	3,287	1.794-6.022
Adrenal gland metastasis: none	0.001	0.001	3,187	1.678-6.051
irAEs: grade 2-4	0.955			
Atezolizumab-containing therapy: first line	0.018	0.003	2,814	1.420-5.574
Regimen: PTX-regimen	0.2720			

CI: Confidence interval; PS: performance status; PD-L1: programmed death-ligand 1; irAE: immune-related adverse events; PTX: paclitaxel.

Table IV. *Uni- and multivariate analyses of favorable factors in overall survival.*

	Analysis			
	Univariate	Multivariate		
Factor	*p*-Value	*p*-Value	Hazard ratio	95%CI
Sex: Female	0.385			
PS: 0	0.027	0.132	1.684	0.855-3.319
Age: less than 70 years	0.168			
PD-L1: positive	0.354			
Stage: IIIA-C	0.218			
Pathology: Adenocarcinoma	0.846			
Brain metastasis: none	0.891			
Liver metastasis: none	0.001	0.001	2.917	1.578-5.392
Adrenal gland metastasis: none	0.001	0.001	3.204	1.641-6.255
irAEs: grade 2-4	0.989			
Atezolizumab-containing therapy: first line	0.747			
Regimen: PTX-regimen	0.917			

CI: Confidence interval; PS: performance status; PD-L1: programmed death-ligand 1; irAE: immune-related adverse events; PTX: paclitaxel.

the presence or absence of brain metastasis did not have a significant effect on prognosis. Further accumulation of prognostic analyses that take into account information on metastasis is anticipated.

Regarding irAEs, additional caution is required when ICIs are used in combination with chemotherapy. In clinical trials and real-world studies of combination therapies with anti-PD-1 antibodies, grade 3 or higher irAEs and grade 5 irAEs were observed in 18.3% to 74.8% of patients and grade 5 irAEs were observed in 1.2% to 6.7% of patients. Pulmonary irAEs were found in 0.7%-10.1% of patients (8, 18-23). In three clinical trials on atezolizumab plus chemotherapy, 24.0% to 54.6% of patients had irAEs of grade ≥3, and grade 5 irAEs developed in 2.0% to 6.1% of patients. Pulmonary irAEs were seen in 0.5%-6.2% of patients (3-6). Ikeuchi *et al*. reported pulmonary irAEs in 3.3% of patients treated with atezolizumab plus chemotherapy in clinical practice (24). There have been no reports of irAEs of any grade or grade ≥3 in real-world clinical practice (24). In the present study, irAEs of grade 3 or higher were observed in 9.9% of the patients and grade 5 in 2.1% of the patients. Grade 5 pulmonary irAEs were identified in 1.4% of the patients. These results were

Table V. *Logistic regression analysis in patients with overall survival ≥3 years or <3 years.*

Factor	*p*-Value	Hazard ratio	95%CI
Sex: Female	0.918	0.94	0.26-3.37
PS: 0	0.041	3.05	1.05-8.88
Age: less than 70 years	0.957	1.03	0.38-2.78
PD-L1: positive	0.392	1.57	0.56-4.44
Stage: IIIA-C	0.581	1.52	0.35-6.62
Brain metastasis: none	0.798	1.19	0.32-4.42
Liver metastasis: none	0.272	3.38	0.39-29.71
Adrenal gland metastasis: none	0.998	1.00	0.18-5.62
Pathology: Adenocarcinoma	0.557	0.70	0.22-2.28
irAEs: grade 2-4	0.698	1.62	0.51-5.16
Treatment line: first	0.809	0.81	0.14-4.53
Regimen: PTX-regimen	0.664	1.69	0.48-5.97

CI: Confidence interval; PS: performance status; PD-L1: programmed death-ligand 1; irAE: immune-related adverse events; PTX: paclitaxel.

similar to those of previous clinical trials and real-world investigations (8, 18-23). In our study, irAEs of all grades were observed in 25.4% of patients. Although the incidence of irAEs appeared to be low, the possibility of under-evaluation in retrospective studies could not be ruled out.

This study on the use of combined atezolizumab plus chemotherapy in clinical practice is a significant investigation, involving over 100 patients. However, this study has limitations that should be mentioned. It was a retrospective study and included patients with a wide range of background characteristics. It is important to compare the OS and PFS between patients who received combined atezolizumab plus chemotherapy and those who received chemotherapy alone as controls. However, selection bias due to background factors (presence or absence of pulmonary fibrosis, difference in PS, *etc.*) when selecting treatment might be a major obstacle in comparing OS and PFS. Although this selection bias makes it difficult to perform such comparisons in clinical practice, it is important to know the results of such comparisons. With regard to driver genes, new driver gene evaluations, such as *ROS1*, *BRAF*, and *KRAS*, became available in clinical practice during the study period, but these genes could not be evaluated equally in all patients. It has also been suggested that TTF-1, LKB1, and KEAP1 may provide important information regarding the therapeutic effects of ICIs in the future (26). Analysis including information on these new driver genes is a future task.

In our routine practice, PFS and OS with combined atezolizumab plus chemotherapy were found to be comparable to the results reported in published trials. With regard to the frequency and severity of irAEs, our results were consistent with those previously reported in trials and clinical practices involving ICI plus chemotherapy, suggesting that long-term administration may be feasible for certain patients. It is necessary to pay close attention to irAEs and assemble and utilize actual clinical results to maximize the efficacy of combination therapy, including those containing atezolizumab. Elucidation of factors contributing to long-term responses, with a focus on information regarding metastatic organs, would have a beneficial impact on clinical practice.

Conflicts of Interest

The Authors declare that they have no competing interests in relation to this study.

Table VI. *Immune-related adverse events (irAEs).*

Number of irAE	Number of patients who had irAE	irAE	Number of patients	Grade				
				1	2	3	4	5
Not developed	102	Pulmonary	14	3	6	2	1	2
Developed	39 (27.7%)	Skin	5	1	0	4	0	0
		Thyroid	6	2	4	0	0	0
		Adrenal gland	3	0	3	0	0	0
Number of irAE		Pituitary gland	1	0	1	0	0	0
One	32	Diabetes	4	0	4	0	0	0
Two	6	Neurotoxicity	2	1	0	0	1	0
Three	1	SIADH	1	0	0	1	0	0
Total	47	Hepatobiliary	4	3	0	1	0	0
		Gastrointestinal	4	1	2	1	0	0
		Musculoskeletal	2	1	1	0	0	0
		Sepsis	1	0	0	0	0	1
		Total	47	12	21	9	2	3

SIADH: Syndrome of inappropriate secretion of antidiuretic hormone.

Authors' Contributions

TN, RN, GO, and HS designed this study. TN, TS, HW, GO, TT, NK, KM, SH, TY, KK, MI, HS, TK, and TE collected data. TN, RN, SO, GO, and HS analyzed the data. TN, RN, GO, HS, and NH prepared the manuscript. HS and NH supervised this study. All Authors have approved the final version of the manuscript for submission.

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