

Promising Effectiveness of Combined Chemotherapy and Immunotherapy in Patients with Advanced Non-small Cell Lung Cancer: A Real-World Prospective Observational Study (CS-Lung-003)

Nobuhiro Kanaji^{a*}, Kazuya Nishii^b, Yukari Tsubata^c, Mika Nakao^c,
Takae Okuno^c, Sachi Okawa^d, Kenji Takata^d, Masahiro Kodani^e,
Masahiro Yamasaki^f, Kazunori Fujitaka^g, Tetsuya Kubota^h, Masaaki Inoueⁱ,
Naoki Watanabe^a, and Katsuyuki Hotta^j; CS-Lung-003 Investigator

^aDepartment of Internal Medicine, Division of Hematology, Rheumatology and Respiratory Medicine, Faculty of Medicine, Kagawa University, Miki-cho, Kagawa 761-0793, Japan,

^bDepartment of Respiratory Medicine, National Hospital Organization Iwakuni Clinical Center, Iwakuni, Yamaguchi 740-8510, Japan,

^cDepartment of Internal Medicine, Division of Medical Oncology and Respiratory Medicine, Shimane University Faculty of Medicine, Izumo, Shimane 693-8501, Japan,

^dDepartment of Allergy and Respiratory Medicine, ^jCenter for Innovative Clinical Medicine, Okayama University Hospital, Okayama 700-8558, Japan,

^eDivision of Medical Oncology and Molecular Respiriology, Faculty of Medicine, Tottori University, Yonago, Tottori 683-8503, Japan,

^fDepartment of Respiratory Disease, Hiroshima Red Cross Hospital and Atomic-Bomb Survivors Hospital, Hiroshima 730-8619, Japan,

^gDepartment of Molecular and Internal Medicine, Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima 734-8553, Japan,

^hDepartment of Respiratory Medicine and Allergology, Kochi University, Nankoku, Kochi 783-8505, Japan,

ⁱDepartment of Chest Surgery, Shimonoseki City Hospital, Shimonoseki, Yamaguchi 750-8520, Japan

This prospective observational study investigated the clinical status of patients with advanced non-small cell lung cancer (NSCLC) treated with cytotoxic chemotherapy + an immune checkpoint inhibitor (chemo+IO) as first-line treatment in a real-world setting. The cases of 98 patients treated with chemo+IO were prospectively collected and analyzed for effectiveness and safety. The response rate to chemo+IO was 46.9%, and the disease control rate was 76.5%. The median progression-free survival and overall survival (OS) in the total population were 5.2 and 22.3 months, respectively. The patients positive for PD-L1 ($\geq 1\%$) showed significantly longer OS than the negative group ($< 1\%$) (median 26.7 vs. 18.7 months, $p=0.04$). Pre-existing interstitial lung disease (ILD) was associated with shorter OS than the absence of ILD (median 9.0 vs. 22.6 months, $p<0.01$). Immune-related adverse events (irAEs) were observed in 28 patients (28.6%). The most frequent irAE was ILD ($n=11$); Grade 1 ($n=1$ patient), G2 ($n=5$), G3 ($n=4$), and only a single patient with a G5 irAE. In this CS-Lung-003 study, first-line chemo+IO in a real-world setting showed good effectiveness, comparable to that observed in international clinical trials. In real-world practice, chemo+IO is a promising and steadfast strategy.

Key words: non-small cell lung cancer, real-world, first-line, immune checkpoint inhibitor, combined immunotherapy

Results from several clinical trials have established the combination therapy of cytotoxic anticancer agents and immune checkpoint inhibitors (ICIs) (chemo+IO) as one of the standard first-line treatments for advanced non-small cell lung cancer (NSCLC) [1-4]. These trials reported median progression-free survival (PFS) ranging from 6.4 to 9.0 months and overall survival (OS) ranging from 15.9 to 22.0 months in their chemo+IO groups. However, the trials had strict enrollment criteria that included adequate organ function and good performance status (PS) in order to ensure efficacy and safety. In real-world practice, many patients do not meet the criteria for trial enrollment. It has been reported that only 30% of advanced lung cancer patients are eligible for ICI trials [5]. There has been a lack of data on patients receiving chemo+IO in real-world settings, but recent data indicate that real-world patients undergoing immunotherapy may achieve shorter survival periods than trial participants [5, 6].

Given this background, we initiated a prospective observational study to investigate the clinical status in advanced NSCLC patients treated with chemo+IO as the first-line treatment in a real-world setting.

Patients and Methods

Patients and study design. Patients with NSCLC were prospectively recruited from an umbrella-type prospective lung cancer patient registry in Japan (CS-Lung-003; UMIN000026696) starting in March 2017 [7]. This registry encompassed various prospective observational studies aimed at elucidating multiple clinical practice patterns in lung cancer treatment [8], including the present study. This study focused on advanced NSCLC patients who received chemo+IO as

the first-line treatment, aiming to uncover the true status of therapeutic regimens, as well as the regimens' efficacy and safety. Data for this study were collected from January 2019 to August 2021. The study protocol was approved by the ethics committees of all affiliated hospitals (no. 1703-055; Institutional Review Board of Okayama University Hospital), and written informed consent was obtained from all patients. Patients who met any of the following criteria were excluded: (i) receiving definitive thoracic irradiation, (ii) receiving any treatment other than chemo+IO as the first-line therapy, or (iii) having any mutations or fusions of driver genes, such as epidermal growth factor receptor. Patients who received palliative radiation therapy were included.

Statistical analyses. PFS was defined as the time between the start of a chemo+IO regimen and the diagnosis of disease progression or death from any cause, while OS was defined as the time between the date of diagnosis and date of death from any cause. PFS and OS curves were constructed by the Kaplan–Meier method, and differences in survival were compared using the log-rank test. Fisher's exact test, the χ^2 -test, and Student's *t*-test were used to analyze the patient characteristics and therapeutic efficacy. All statistical analyses were performed using Ekuseru-Toukei 2015 (Social Survey Research Information, Tokyo).

Results

Patient characteristics. Of the 1,463 patients with pathologically confirmed advanced NSCLC registered in the CS-Lung-003 study, a total of 98 patients receiving chemo+IO were registered in the present study (Fig. 1). Table 1 summarizes the patients' charac-

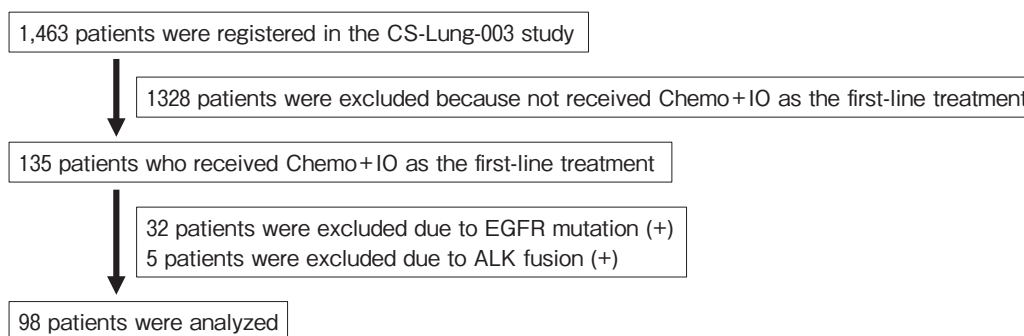


Fig. 1 Flow diagram of the patient enrollment.

Table 1 Patient and tumor characteristics

Characteristic	n=98
Age, median (range)	69 (45–82)
Gender, male/female	86/12
Smoking history, smoker/never smoker	85/13
Pack-years in smokers, average (range)	54 (5–174)
ECOG performance status, 0/1/2/3/4/unknown	44/45/5/2/0/2
Histology, adenocarcinoma/squamous cell carcinoma/others	60/32/6
Clinical stage, IIIA/IIIB/IIIC/IVA/IVB	10/6/6/34/42
PD-L1 TPS (%), <1/1–49/50≤/unknown	29/20/21/28
Palliative irradiation prior to first-line therapy, yes/no	15/83
First-line therapeutic regimen	
Carboplatin + pemetrexed + pembrolizumab	34
Carboplatin + nab-paclitaxel + pembrolizumab	24
Cisplatin + pemetrexed + pembrolizumab	11
Carboplatin + paclitaxel + pembrolizumab	9
Carboplatin + paclitaxel + bevacizumab + atezolizumab	8
Carboplatin + pemetrexed + atezolizumab	4
Others	8

ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed cell death-ligand 1; TPS, tumor proportion score.

teristics. Prior to first-line therapy, 15 of the patients received palliative irradiation, in the chest (n=9) or the brain (n=4). Among the selected first-line chemo+IO regimens, pembrolizumab-containing regimens were the most common, with 34 patients receiving carboplatin + pemetrexed + pembrolizumab and 24 patients receiving carboplatin + nab-paclitaxel + pembrolizumab.

Responses to first-line therapy. Response data to first-line therapy were available for 81 patients, among whom the response rate was 46.9% and the disease control rate was 76.5% (Table 2). There were no significant differences in response rates among the patients or the tumor characteristics, including PS, programmed cell death-ligand 1 (PD-L1) expression, and palliative irradiation prior to chemo+IO. The following response rates were observed; carboplatin + pemetrexed + pembrolizumab, 57.7%; carboplatin + nab-paclitaxel + pembrolizumab, 45.0%; and cisplatin + pemetrexed + pembrolizumab, 33.3%, with no significant differences observed.

The patients' PFS and OS. The median PFS of the 98 patients was 5.2 months. There were no significant differences in PFS among the patients or the tumor characteristics, including age, histology, performance status, and PD-L1 expression (Table 3). The patients who underwent palliative irradiation prior to first-line chemo+IO showed a tendency towards longer PFS

compared to the patients without irradiation (median 7.7 vs. 4.7 months, $p=0.10$). The median OS in the total population was 22.3 months (Table 4). The patients with PD-L1 positivity ($\geq 1\%$) had longer OS compared to those with PD-L1 negativity ($< 1\%$) (median 26.7 vs. 18.7 months, $p=0.04$). The patients with pre-existing interstitial lung disease (ILD) had shorter OS compared to those without ILD (median 9.0 vs. 22.6 months, $p<0.01$).

The safety of the chemo+IO regimens. Adverse events (AEs) were reported in 52 (53.1%) of the 98 patients (Table 5). Febrile neutropenia was observed in 11 patients (11.2%), with one case being classified as grade 5. Immune-related AEs (irAEs) were observed in 28 patients (28.6%). The most frequent irAE was ILD (n=11; 11.2%), followed by rash, hypothyroidism, hepatitis, colitis, adrenal insufficiency, and others (Table 5). Treatment-related ILDs were diagnosed by respiratory specialists at each institute based on the patients' clinical features, radiologic findings, and bronchoscopic examination when available. The ILD grades were G1 (n=1 patient), G2 (n=5), G3 (n=4), and G5 (n=1), the latter of whom was the only patient with a G5 irAE. There was no significant difference in PFS between the patients with or without an irAE ($p=0.94$, median 7.2 vs. 5.0 months, respectively, Table 3).

Table 2 Response to first-line therapy

Characteristic	Response to first-line therapy				
	n	CR/PR/SD/ PD/NE (n)	Response rate (%)	Disease control rate (%)	P-value
All patients	98	2/36/24/19/17	46.9	76.5	
Age					
< 75	80	1/29/22/15/13	44.8	77.6	
≥ 75	18	1/7/2/4/4	57.1	71.4	0.50
Gender					
Male	86	2/33/21/14/16	50.0	80.0	
Female	12	0/3/3/5/1	27.3	54.6	0.29
Smoking history					
Smoker	85	2/34/21/13/15	51.4	81.4	
Never smoker	13	0/2/3/6/2	18.2	45.5	0.10
ECOG performance status					
0-1	89	2/34/21/17/15	48.0	77.3	
2-4	7	0/1/3/1/2	20.0	60.0	0.49
Histology					
Adenocarcinoma	60	0/23/16/12/9	45.1	76.5	
Squamous cell carcinoma	32	1/11/8/6/6	46.2	76.9	0.70
Clinical stage					
III	22	1/8/5/3/5	52.9	45.3	
IV	76	1/28/19/16/12	45.3	75.0	0.76
PD-L1 TPS (%)					
< 1	28	0/8/9/5/6	36.4	77.3	
1 ≤	41	1/18/9/7/6	54.3	80.0	0.59*
1-49	20	1/6/5/5/3	41.2	70.6	
50 ≤	21	0/12/4/2/3	66.7	88.9	0.25*
ILD					
No	95	2/36/22/18/17	48.7	76.9	
Yes	3	0/0/2/1/0	0	66.7	0.37
Palliative irradiation prior to first-line therapy					
Yes	15	1/5/6/1/2	46.2	92.3	
No	83	1/31/18/18/15	47.1	73.5	0.26
First-line therapeutic regimen					
Carboplatin + pemetrexed + pembrolizumab	34	0/15/6/5/8	57.7	80.8	
Carboplatin + nab-paclitaxel + pembrolizumab	24	1/8/7/4/4	45.0	80.0	0.55**
Cisplatin + pemetrexed + pembrolizumab	11	0/3/3/3/2	33.3	66.7	0.61**

CR, complete response; ECOG, Eastern Cooperative Oncology Group; ILD, interstitial lung disease; NE, not evaluated; PD, progressive disease; PD-L1, programmed cell death-ligand 1; PR, partial response; SD, stable disease; TPS, tumor proportion score.

*v.s. < 1%, **v.s. carboplatin + nab-paclitaxel + pembrolizumab

Second-line chemotherapy. Forty-six patients (47.0%) received second-line chemotherapy (Table 6). Docetaxel was the most frequently used agent (n = 29), including 18 patients who received it in combination with ramucirumab. The response rate to second-line chemotherapy was 25.0% for all 46 patients and 31.8% for the patients treated with docetaxel with or without ramucirumab. No serious AEs, including ILD, were

reported in the patients who received second-line chemotherapy.

Discussion

This prospective observational study collected real-world data from 98 patients with advanced NSCLC treated with first-line chemo+IO, including patients

Table 3 Progression-free survival to first-line therapy

Characteristic	n	Median PFS (months)	Univariate analysis (P-value)
All patients	52	5.2	
Age			
< 75	45	5.3	
≥ 75	6	4.7	0.89
Gender			
Male	43	5.8	
Female	8	4.7	0.88
Smoking history			
Smoker	43	6.0	
Never smoker	8	3.7	0.59
ECOG performance status			
0-1	43	5.8	
2-4	6	2.1	0.35
Histology			
Adenocarcinoma	32	5.3	
Squamous cell carcinoma	19	4.5	0.17
Clinical stage			
III	12	6.0	
IV	40	5.0	0.22
PD-L1 TPS (%)			
< 1	17	5.0	
1 ≤	20	6.0	0.13 *
1-49	11	4.1	
50 ≤	9	6.1	0.21 *
ILD			
No	50	5.2	
Yes	2	1.7	0.23
Palliative irradiation prior to first-line therapy			
Yes	13	7.7	
No	39	4.7	0.10
First-line therapeutic regimen			
Carboplatin + pemetrexed + pembrolizumab	17	6.0	
Carboplatin + nab-paclitaxel + pembrolizumab	16	4.5	0.75 **
Cisplatin + pemetrexed + pembrolizumab	6	3.1	0.70 **
Immune-related adverse event			
Yes	13	7.2	
No	38	5.0	0.94

ECOG, Eastern Cooperative Oncology Group; ILD, interstitial lung disease; PD-L1, programmed cell death-ligand 1; TPS, tumor proportion score.

*v.s. <1%, **v.s. carboplatin + nab-paclitaxel + pembrolizumab

with low PD-L1 expression and a poor PS. Our analyses yielded the following findings: (i) the rates of response and disease control to first-line chemo+IO were 46.9% and 76.5%, respectively; (ii) the median PFS and OS were 5.2 and 22.3 months, respectively; (iii) irAEs were observed in 28.6% of the patients, with ILD being the most frequent (11.2%), including one case classified as grade 5; and (iv) the response rate to second-line treatment with docetaxel, with or without ramucirumab,

was 31.8%.

At the time this study was initiated in 2019, there was a lack of data on patients who received chemo+IO in a real-world setting. However, several studies providing insights into this subject subsequently emerged [5, 6, 9-12]. In a retrospective large-scale study of 4,271 patients treated with chemo+IO, the median OS was 10.6 months for the 814 patients with squamous NSCLC and 12.0 months for the 3,457 patients with non-squa-

Table 4 Overall survival

Characteristic	n	Median OS (months)	Univariate analysis (P-value)
All patients	98	22.3	
Age			
<75	80	22.3	
≥75	17	NR	0.49
Gender			
Male	86	22.1	
Female	12	22.3	0.87
Smoking history			
Smoker	85	22.6	
Never smoker	13	20.6	0.57
ECOG performance status			
0-1	89	22.3	
2-4	7	19.1	0.68
Histology			
Adenocarcinoma	60	22.3	
Squamous cell carcinoma	32	19.7	0.74
Clinical stage			
III	22	NR	
IV	76	21.6	0.12
PD-L1 TPS (%)			
<1	29	18.7	
1≤	41	26.7	0.04*
1-49	20	26.7	
50≤	21	23.3	0.11*
ILD			
No	95	22.6	
Yes	3	9.0	<0.01
Palliative irradiation prior to first-line therapy			
Yes	15	19.7	
No	83	23.3	0.49
First-line therapeutic regimen			
Carboplatin + pemetrexed + pembrolizumab	34	21.6	
Carboplatin + nab-paclitaxel + pembrolizumab	24	19.1	0.87**
Cisplatin + pemetrexed + pembrolizumab	11	NR	0.15**
Immune-related adverse event			
Yes	28	19.7	
No	66	22.3	0.98

ECOG, Eastern Cooperative Oncology Group; ILD, interstitial lung disease; PD-L1, programmed cell death-ligand 1; TPS, tumor proportion score.

*v.s. <1%, **v.s. carboplatin + nab-paclitaxel + pembrolizumab

mous disease [6]. These survival rates were lower than those reported in pivotal clinical trials. An investigation of the differences in survival based on whether the patients met the criteria for enrollment in clinical trials revealed that the median OS was 10.2 months for the total population and was numerically longer for the patients who met the criteria for clinical trial enrollment compared to those who did not (median OS 13.1 vs. 8.8 months, $p=0.10$) for first-line ICI (ICI mono-

therapy or chemo+IO) [5].

In a U.S. study of 283 patients with Eastern Cooperative Oncology Group (ECOG) PS 0-1 who were treated with carboplatin + pemetrexed + pembrolizumab, the median PFS and OS were 6.4 and 16.5 months, respectively [9]. When stratified by PD-L1 expression, the median OS was 20.6, 16.3, and 13.2 months for the patients with PD-L1 ≥50%, 1-49%, and <1%, respectively [9]. Another retrospective analysis of

Table 5 Adverse events

AE	Grade (n, %)					
	Any	1	2	3	4	5
Hematologic AE						
Neutropenia	15 (15.3)			10	5	
Febrile neutropenia	11 (11.2)			7	3	1
Anemia	5 (5.1)	1	3	1		
Thrombocytopenia	6 (6.1)	1	4	1		
Non-hematologic AE						
Proteinuria	6 (6.1)	2	3	1		
Hypertension	4 (4.1)		3	1		
Appetite loss	3 (3.1)		1	2		
General fatigue	2 (2.0)			2		
Oral mucositis	1 (1.0)			1		
Nausea	1 (1.0)			1		
Diarrhea	1 (1.0)			1		
Creatinine increase	4 (4.1)	3	1			
Creatine kinase increase	1 (1.0)			1		
AST increase	1 (1.0)			1		
ALT increase	1 (1.0)			1		
Hyponatremia	1 (1.0)			1		
Peripheral edema	2 (2.0)		2			
Pleural effusion	2 (2.0)		2			
Peripheral neuropathy	1 (1.0)		1			
Immune-related AE						
Interstitial lung disease	11 (11.2)	1	5	4		1
Rash	6 (6.1)					
Hypothyroidism	2 (2.0)					
Hepatitis	2 (2.0)					
Colitis	2 (2.0)					
Adrenal insufficiency	2 (2.0)					
Hypopituitarism	1 (1.0)					
Renal dysfunction	1 (1.0)					
Unknown	3 (3.1)					

AE, adverse event; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

PD-L1-positive NSCLC reported longer median OS with chemo+IO (19.8 months, n=136) compared to chemotherapy alone (11.2 months, n=128) [10]. In a study targeting PD-L1 expression $\geq 50\%$, better survival was observed with the median OS values of 21.0 months for chemo+IO and 22.1 months for ICI monotherapy) [11]. These reports indicate that real-world data on chemo+IO generally show lower effectiveness compared to the clinical trials, but as in the clinical trials, the effectiveness of treatment depends on the patient's PD-L1 expression.

The results of this study demonstrated that the median PFS (5.2 months) and OS (22.3 months) are comparable to the results reported in pivotal international clinical trials, despite the inclusion of patients

with low PD-L1 expression and poor PS. One possible reason for this improved effectiveness could be related to ethnicity or the healthcare system in Japan. It has been observed that Japanese sub-analyses of international clinical trials or Japanese-specific trials tend to show better outcomes compared to the overall trial population in international trials [13,14]. Moreover, a retrospective study conducted in Japan evaluating platinum + pemetrexed + pembrolizumab reported favorable outcomes, with a median PFS of 8.6 months and OS that has not been reached (with a range of 15.7 months to 'not reached') [12]. These findings suggest that the effectiveness of chemo+IO in the Japanese population may be higher compared to other populations, highlighting the importance of considering regional

Table 6 Status of second-line chemotherapy

Characteristic	n=46 (47.0%)
Age, average (range)	68 (45–82)
Gender, male/female	40/6
Smoking history, smoker/never smoker	39/7
Pack-years in smokers, average (range)	57 (5–174)
ECOG performance status, 0/1/2/3/4/unknown	10/25/9/1/0/1
Histology, adenocarcinoma/squamous cell carcinoma/others	28/17/1
PD-L1 TPS (%), <1/1–49/50≤/unknown	16/9/8/13
Second-line therapeutic regimen	
Docetaxel + ramucirumab	18
Docetaxel	11
S-1	9
Nab-paclitaxel	5
Others	3
Efficacy (all patients)	
CR/PR/SD/PD/NE	1/7/7/17/14
Response rate (%)/ Disease control rate (%)	25.0/46.9
PFS, median months	2.1
Efficacy (docetaxel with or without ramucirumab)	
CR/PR/SD/PD/NE	0/7/4/11/7
Response rate (%)/ Disease control rate (%)	31.8/50.0
PFS, median months	2.1

CR, complete response; ECOG, Eastern Cooperative Oncology Group; NE, not evaluated; PD, progressive disease; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival; PR, partial response; SD, stable disease; TPS, tumor proportion score.

factors in assessing treatment outcomes.

In the real-world setting of this study, multiple chemo+IO regimens were selected. Among these regimens, pembrolizumab-containing regimens emerged as the most commonly chosen options. This preference for pembrolizumab-containing regimens suggests that physicians and patients have confidence in the effectiveness and safety of these regimens. Due to the inherent selection bias resulting from the diverse backgrounds of the patients in this study, it was not possible to directly compare the treatment effectiveness of different regimens. However, the overall findings that we obtained indicate that the selected treatments were effective in a real-world setting. Additionally, no significant differences were observed in the frequency of irAEs among the different regimens, suggesting comparable safety profiles.

In several clinical trials, adverse events associated with the use of chemo+IO have occurred in >95% of the patients [1-3]. The high-frequency adverse events included hematological and gastrointestinal toxicities. The frequency of adverse events in the present study was

lower (53.1%) than in these clinical trials. This may be due to the fact that some adverse events, especially mild ones, were not reported by the treating physicians. For example, in the KN-189 trial anemia and constipation were reported in 46.2% and 34.8% of the patients, respectively, [1], whereas the corresponding values in the present study were 5.1% and 0%. The incidence of ILD in the present series was high at 11.2%, however. This is probably due to in large part to the regional (ethnic) origin of Japanese patients. A retrospective observational analysis of the use of pembrolizumab + chemotherapy in Japan reported 18% as the frequency of ILD [12]. In that study [12] and the present investigation, 1% of patients died of ILD, and thus close attention should be paid to the development of ILD.

We observed a favorable response to second-line treatment with docetaxel with or without ramucirumab, with a response rate of 31.8%. This finding is consistent with several retrospective studies that have reported high efficacy of docetaxel+ramucirumab after ICI treatment, with response rates ranging from 32.5% to 60.0% [15-17], while in the REVEL study without ICI

pretreatment, the response rate was 23% [18]. Similarly, a prospective phase II study investigating nab-paclitaxel in patients previously treated with an ICI showed a higher response rate at 55.2% [19]. However, when a propensity score analysis was used to adjust for potential confounding factors, the advantages in PFS and OS were not demonstrated. This suggests that the synergistic antitumor effect observed with chemotherapy following ICI treatment may be transient [20]. It should be noted that in the mentioned phase II study, the PFS tended to be better than that in the earlier report by the same research group, indicating potential improvements in outcomes (5.6 vs. 3.9 months) [19]. However, further studies are needed to fully understand the impacts of chemotherapy administered after ICI treatment on the patients' long-term prognosis and to clarify the optimal sequencing and combination strategies for maximizing treatment efficacy in patients with advanced NSCLC.

The study has several limitations that should be considered. The sample size was small ($n=98$), which may limit the generalizability of the findings. A larger sample size would have provided a more robust analysis and potentially allowed for more detailed subgroup analyses based on patient characteristics. There were also limitations related to data collection. Some information (such as the grades of irAEs other than ILD) was not available. Lastly, the study lacked long-term follow-up data, which could have provided insights into the durability of treatment responses and survival outcomes.

In conclusion, this multicenter prospective study obtained evidence that first-line chemo+IO in a real-world setting is effective and comparable to the results seen in pivotal international clinical trials. Our findings also demonstrated that the patients treated with second-line docetaxel+ramucirumab had a favorable response rate. These findings support the use of chemo+IO as a promising treatment regimen for advanced NSCLC in routine clinical practice. The results of this study contribute to the growing body of evidence supporting the efficacy and feasibility of treatment with cytotoxic chemotherapy + an immune checkpoint inhibitor in real-world patient populations.

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