INNOVATIONS JOURNALS

Research Article

Treatment of Stage IV Non–Small Cell Lung Cancer with Pembrolizumab in Combination with Platinum-Based Doublet Chemotherapy in Vietnam

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Source of Support: None. Conflict of Interest: None.

Received: May 2, 2023; Revision Received: Jun 11, 2023; Accepted: Jun 17, 2023

Nguyen TK, Ta TV. Treatment of stage IV non–small cell lung cancer with pembrolizumab in combination with platinum-based doublet chemotherapy in Vietnam. *J Immunother Precis Oncol*. 2023; 6:133–140. DOI: 10.36401/JIPO-23-12.

ABSTRACT

Introduction: Lung cancer has been one of the most prevalent cancers worldwide in recent decades. According to the findings of the KEYNOTE-407 (2018) study on patients with stage IV squamous cell lung cancer, the combination of pembrolizumab and chemotherapy in the first-line treatment prolongs overall survival compared with chemotherapy alone. This study aimed to evaluate the efficacy and side effects of treating patients with stage IV non–small cell lung cancer with pembrolizumab in combination with platinum-based doublet chemotherapy. **Methods:** A retrospective multicenter study on 46 patients at four hospitals in Vietnam between June 2018 and August 2022. Patients received first-line treatment with a protocol of pembrolizumab in combination with platinum-based doublet chemotherapy (pemetrexed plus carboplatin or paclitaxel plus carboplatin). The study's primary endpoints were progression-free survival and safety. The secondary endpoint was overall survival. **Results:** The median progression-free survival was 11.0 months (95% CI, 7.4–14.7 months). The median overall survival was 23.1 months (95% CI, 18.4–27.8 months). The survival rate of patients after 1 and 2 years was 82.3% and 43.3%, respectively. The most common side effects were anemia and elevated liver enzymes, but they were primarily mild or moderate severity. Progression-free survival did not depend on cancer type based on histology ($p = 0.13$). The progression-free survival was independent of programmed death ligand-1 expression levels $< 50\%$ or $\geq 50\%$ ($p = 0.68$). **Conclusion:** Treatment of stage IV non–small cell lung cancer without *EGFR* and *ALK* gene mutations with the immunotherapy protocol of pembrolizumab in combination with platinum-based doublet chemotherapy resulted in favorable outcomes without any new safety concerns. A larger sample size and longer follow-up in the future are necessary to yield more complete results.

Keywords: non–small-cell lung cancer, immunotherapy, pembrolizumab

INTRODUCTION

Lung cancer has been among the most prevalent cancers worldwide in recent decades. According to GLOBOCAN, there were approximately 2,206,771 new cases worldwide in 2020, accounting for 11.4% of patients with cancer, ranking second after those with breast cancer. Vietnam detected 26,262 new cases, representing 14.4%, and 23,797 patients with lung cancer died.[1] This is a burden for the healthcare system.

Lung cancer consists of two main histologic groups: non–small cell lung cancer (NSCLC; 85%) and small cell lung cancer (10–15%).[2] It is noted that 15–20% of patients with NSCLC are still operable. Targeted drug therapy and immunotherapy are the optimal options for patients with late-stage disease.[3] Immunotherapy is associated with the autologous immune system, which inhibits one or more factors that suppress the body's natural immune system against cancer cells.[4] The KEYNOTE-189 study included patients with stage IV lung cancer with adenocarcinoma, expressed at different levels ($< 1\%$, $\geq 1\%$, 1–49%, $\geq 50\%$), showing progression-free survival (PFS) of 8.8 months in the pembrolizumab plus chemotherapy group compared with 4.9 months in the placebo plus chemotherapy group.[5]

According to the findings of the KEYNOTE-407 (2018) study on patients with stage IV squamous cell lung cancer, the combination of pembrolizumab and chemotherapy in the first-line treatment prolongs overall survival compared with chemotherapy alone.[6]

In Vietnam, there are currently no trials investigating the efficacy of immunotherapy in conjunction with chemotherapy for NSCLC. Therefore, we conducted this study to examine the effectiveness of the first-line treatment of patients with stage IV NSCLC with pembrolizumab in combination with platinum-based doublet chemotherapy at hospitals in Vietnam.

METHODS

A retrospective, multicenter study was conducted to evaluate the efficacy and safety of pembrolizumab in combination with platinum-based doublet chemotherapy in patients with NSCLC. The study's primary endpoints were PFS and safety. The secondary endpoint was overall survival (OS). The study protocol was approved by the institutional review board of Hanoi Medical University (Code HMUIRB485). Patients provided written informed consent before participating in the study. Data and information of patients were confidential and not disclosed for any purposes.

Patients aged 18 or older were eligible for enrollment if they had histologically confirmed stage IV NSCLC without mutations in *EGFR* and *ALK* genes[7] and had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1.[8] They also had to have measurable target lesions and programmed death ligand-1 (PD-L1) test results. Patients were excluded if they had previously undergone systemic cancer therapy, had a life expectancy less than 3 months, had secondary cancer, or systemic immune disease and received corticosteroids. Patients were also excluded if they dropped out of treatment for no professional reason (i.e., when the disease had not progressed and they had no serious adverse effects), were noncompliant, or could not be monitored.

The research was performed between June 2018 and August 2022 in four hospitals in Vietnam, including Vietnam National Cancer Hospital, Bach Mai Hospital, Central Lung Hospital, and Nghe An Oncology Hospital.

Treatment Protocol

Patients received first-line treatment with pembrolizumab in combination with platinum-based doublet chemotherapy according to one of two protocols. The thoracic subcommittee, composed of medical oncologists, surgeons, radiation therapists, radiologists, pathologists, nutritionists, and others, determined the treatment protocol and number of cycles of combination chemotherapy for each patient. They considered the cancer type based on histology, the drug supply status, the patient's financial situation (Vietnam Health Insurance only covers 50% of the cost of pemetrexed), and the patient's response to medication.

The first treatment protocol was as follows:

- Pembrolizumab (200 mg) was administered intravenously on day 1 of each 21-day cycle for up to 35 cycles.
- Pemetrexed (500 mg/m^2) was administered intravenously on day 1 of each 21-day cycle for up to 35 cycles.
- Carboplatin (area under the curve [AUC] 5) was administered intravenously on day 1 of each 21-day cycle for 4 or 6 cycles.

The second treatment protocol was as follows:

- Pembrolizumab (200 mg) was administered intravenously on day 1 of each 21-day cycle for up to 35 cycles.
- Paclitaxel (200 mg/m^2) was administered intravenously on day 1 of each 21-day cycle for 4 or 6 cycles.
- Carboplatin (AUC 6) was administered intravenously on day 1 of each 21-day cycle for 4 or 6 cycles.

Assessments

Evaluation of PD-L1 expression level was performed using the 22C3 PharmDx (Agilent) and SP263 (Ventana) Assays. Evaluation of response to treatment was based on RECIST 1.1 criteria.[9] Time of assessment by imaging at a time after 6 weeks (42 ± 7 days) and 12 weeks (84 ± 7 days) with a 4-cycle protocol, or 9 weeks (63 ± 7 days) and 18 weeks (126 ± 7 days) with a protocol for 6 cycles of combination immunotherapy with platinum-based doublet chemotherapy. Follow-up assessment every 9 weeks (63 ± 7 days) of maintenance therapy. All adverse events and side effects were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events.[10]

PFS per response evaluation criteria in solid tumors (RECIST 1.1) as assessed by blinded central imaging. PFS was defined as the time from treatment allocation to the first documented progressive disease (PD) or death due to any cause, whichever occurred first. Per RECIST 1.1, PD was defined as ≥ 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study. In addition to the relative increase of 20%, the sum must demonstrate an absolute increase of ≥ 5 mm. The appearance of one or more new lesions was also considered PD.

OS was defined as the time from treatment allocation to death due to any cause. Participants without documented death at the time of the interim analysis were censored at the date of the last follow-up.

Data Analysis

The Kaplan–Meier method was used to estimate PFS and OS. To analyze PFS, patients who were alive and had no disease progression or were lost to follow-up were censored at the time of the last tumor assessment. To analyze OS, data for patients who were alive or lost to follow-up were censored at the time of the last contact. The logrank test was used to compare the survival distributions between subgroups.

Table 1. Characteristics of study subjects

Patient Characteristics	*n* (%)
Age (y)	
Mean (range)	59 (34–74)
< 60	23 (50)
≥ 60	23 (50)
Sex	
Male	34 (73.9)
Female	12 (26.1)
ECOG PS	
0	9 (19.6)
1	37 (80.4)
Smoking status	
Ex-smoker and current smoker	26 (56.5)
Never smoked	20 (43.5)
Histology	
Adenocarcinoma	33 (71.7)
Squamous cell carcinoma	9 (19.5)
Not otherwise specified NSCLC	4 (8.8)
Brain metastasis	
Yes	10 (21.7)
No	36 (78.3)
Expression level of PD-L1 (%)	
< 1	13 (28.2)
1–49	24 (52.2)
≥ 50	9 (19.6)

ECOG: Eastern Cooperative Oncology Group; NSCLC: non–small cell lung cancer; PD-L1: programmed death ligand-1; PS: performance status.

RESULTS

Forty-six patients participated in the study, with the shortest follow-up of 3 months and the longest of 32 months. Thirty-three patients had adenocarcinoma, 9 had squamous cell carcinoma, and 4 had not otherwise specified NSCLC (Table 1).

Efficacy

The median PFS was 11.0 months (95% CI, 7.4–14.7 months). The proportion of patients with PFS at 12 and 24 months was 41.4% and 22.2%, respectively. At the end of the study, 17 (36.9%) patients were continuing maintenance therapy (Fig. 1).

PFS did not depend on cancer type based on histology: nonsquamous NSCLC (adenocarcinoma, large cell carcinoma, or unclassified non–small cell carcinoma) or squamous cell carcinoma, with $p = 0.13$ (Fig. 2). The PFS time depended on the treatment protocol of the combination of immunotherapy and initial chemotherapy, with $p < 0.05$ (Fig. 3). The PFS was independent of PD-L1 expression level < 50% or ≥ 50%, with $p = 0.68$ (Fig. 4).

The median OS was 23.1 months (95% CI, 18.4–27.8 months). The percentage of patients surviving at 12, 18, and 24 months was 82.3%, 65.0%, and 43.3%, respectively (Fig. 5).

Safety

Anemia (82.6%), alopecia (69.6%), and gastrointestinal effects (elevated liver enzymes, decreased appetite, nausea, and vomiting) were common side effects. Two (4.3%) patients who discontinued treatment because of tolerability, including one who quit immunotherapy combined with chemotherapy due to severe fatigue and one who developed hepatitis owing to immunotherapy and switched to maintenance therapy with pemetrexed. Grade 3–5 toxicity was observed in 24 (52.2%) patients, and no patient had unacceptable toxicity leading to death (Table 2).

DISCUSSION

The mean age of patients in our study was 59 years old (34–74) (Table 1), much lower than in the KEYNOTE-407 study, whose average age was 65 years old (29–87).[6] This may be because the average age of patients with lung cancer in Vietnam is lower than in developed countries. Dang et al[11] studied more than 350 patients diagnosed with NSCLC by clinical histology from four Vietnamese hospitals; the median age was 61 years. Meanwhile, the average age for lung cancer diagnosis in the United States was 70 years.[12] Besides, the physical condition of older adults in Europe is better than that of Vietnam, so foreign colleagues boldly applied immunotherapy with combination chemotherapy. Doctors in Vietnam often prioritize using monotherapy for patients with NSCLC aged over 75 years . Other studies showed similar results with male predominance, mainly in patients with an ECOG PS score of 1 and in most patients with a history of current or former smoking.

Histologic findings in 71.7% of patients were consistent with adenocarcinoma, while 19.5% had squamous cell carcinoma. Meanwhile, the results of the KEYNOTE-189 study showed that 96.1% of patients had histopathology as adenocarcinoma. This slight difference is because the patients in the study KEYNOTE-189 used only pembrolizumab in combination with pemetrexed and platinum. In contrast, our study used two platinum-doublet chemotherapy regimens in combination with immunotherapy.[5] In our study, the percentage of PD-L1 expression levels ranged from 1% to 49%, accounting for the highest rate of 52.2%, compared with the KEYNOTE-189 study, which reached 31.2%.[5]

The proportion of partial response, stable disease, and progressive disease were 82.6%, 13.0%, and 4.4%, respectively (Fig. 1). Those results were equivalent to the study of Ying Cheng et al,[13] with a total response rate of 80.0% (complete response of 3.1% and partial response of 76.9%). The mean follow-up of the study was 14.9 months. PFS was 11.0 months (95% achieved PFS from 7.4–14.7 months). According to the KEYNOTE-189 study, following up to the time when two-thirds of the patients had severe progression or death, the PFS time was 8.8 months (in which 95% of patients achieved PFS from 7.6–9.2 months).[14] This result is higher than that of KEYNOTE-189 and KEYNOTE-407. The following reasons might explain the difference. First, in our study, 73.9% of patients received combination immunotherapy with chemotherapy for up to six cycles, whereas other studies only allowed for four cycles. Secondly, the time interval for response assessment in our study was

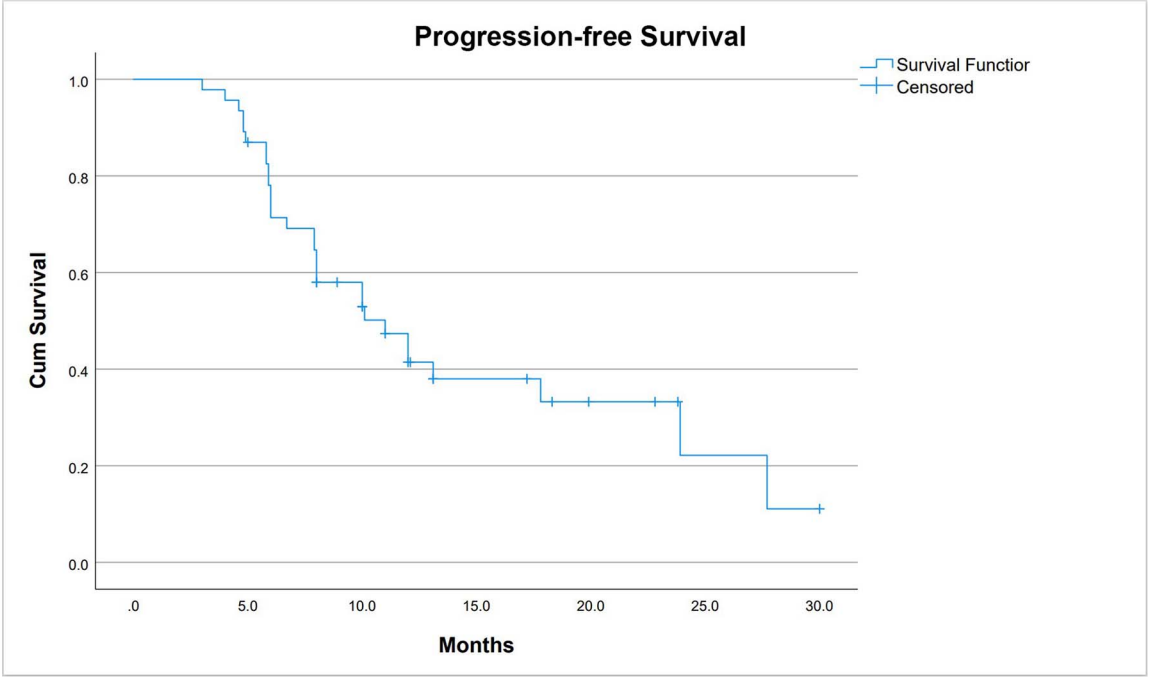

Figure 1. Progression-free survival.

Cum: cumulative.

longer (9 weeks for a protocol that combines immunotherapy with 6 cycles of chemotherapy or maintenance therapy; 6 weeks only for the combination of immunotherapy and 4-cycle chemotherapy), while other studies will assess response at 6 weeks in the combination of immunotherapy phase. Thirdly, the mean age of patients in our study was 59 years, and the oldest patient was 74 years old, which was much lower than the mean age in other studies, such as KEYNOTE-407 (mean age 65–87 years), KEYNOTE-189 (mean age 65–84 years). In addition, there may be other reasons, such as differences in pharmacogenomics in Vietnamese and other Asian populations compared with

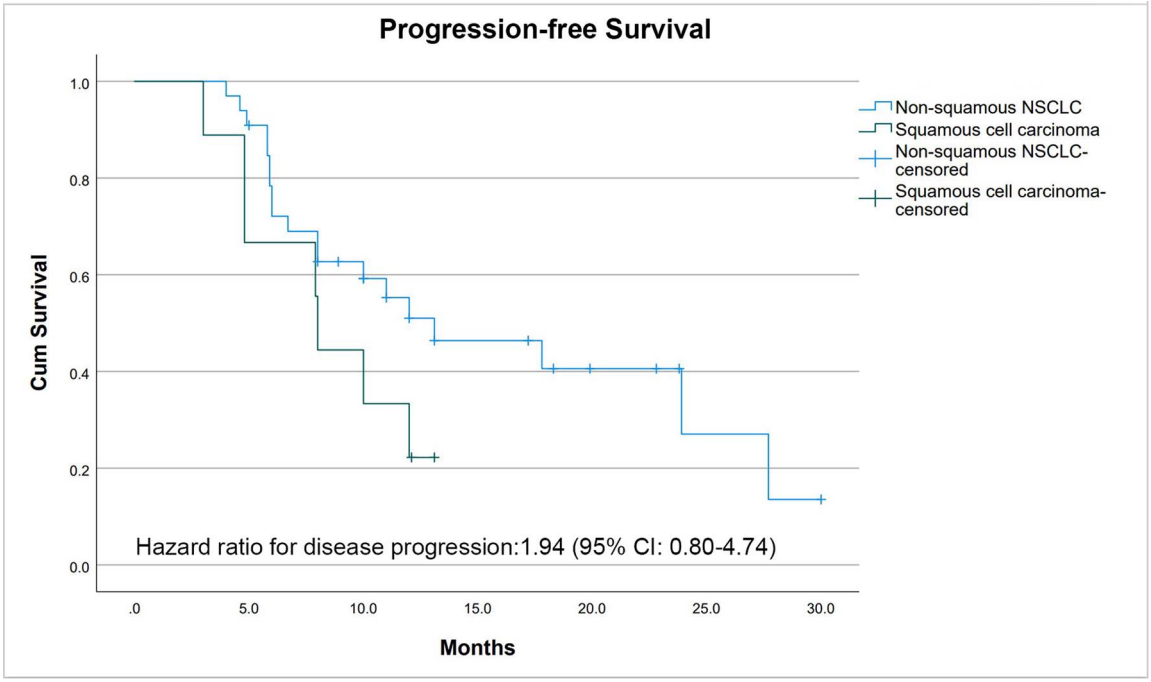

Figure 2. Progression-free survival according to histology.

Cum: cumulative; NSCLC: Non–small cell lung cancer.

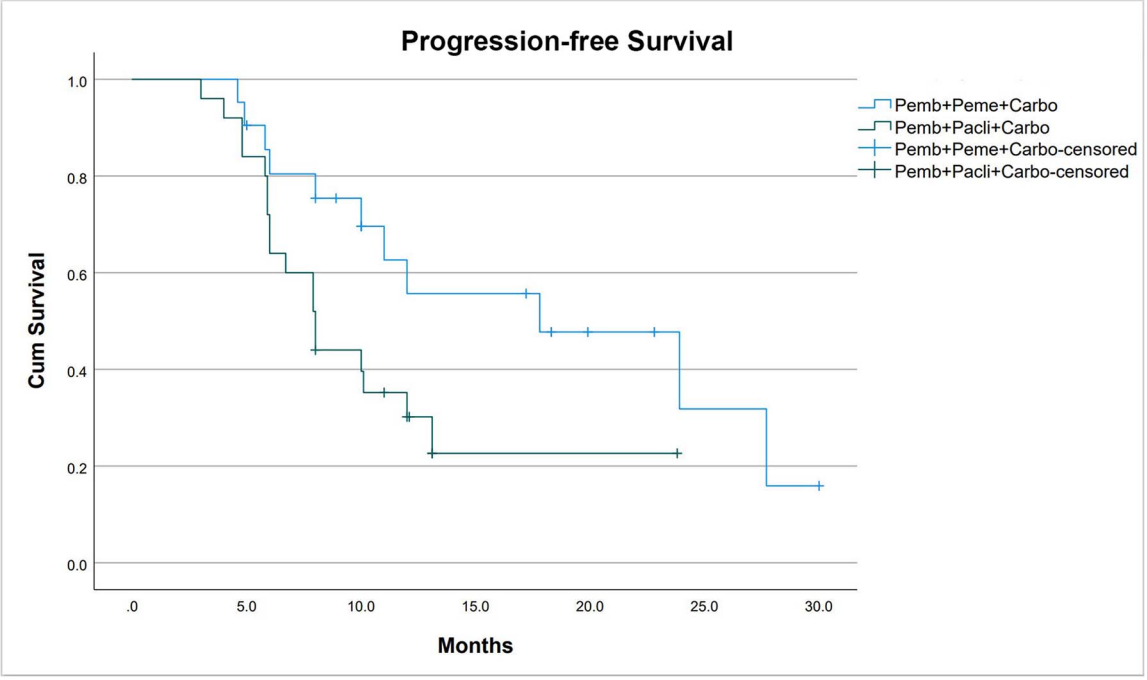

Figure 3. The progression-free survival time according to the treatment protocol.

Carbo: carboplatin; Cum: cumulative; Pacli: paclitaxel; Pemb: pembrolizumab; Peme: pemetrexed.

Whites, but this issue has not been proven. Our study results were lower than those of Horinouchi et al[14] on Japanese patients, with a median PFS of 16.6 months (95% CI, 8.8–21 months). In our study, nearly half of the patients had metastases in two to three locations, and the rate of patients with brain metastases was 21.7%, which was higher than those in the study by Horinouchi et al (16.0%).

The PFS of patients treated with pembrolizumab in combination with pemetrexed and carboplatin was 17.8 months ($n = 21$, 95% CI, 5.3–30.3 months). The group treated with pembrolizumab plus paclitaxel and carboplatin

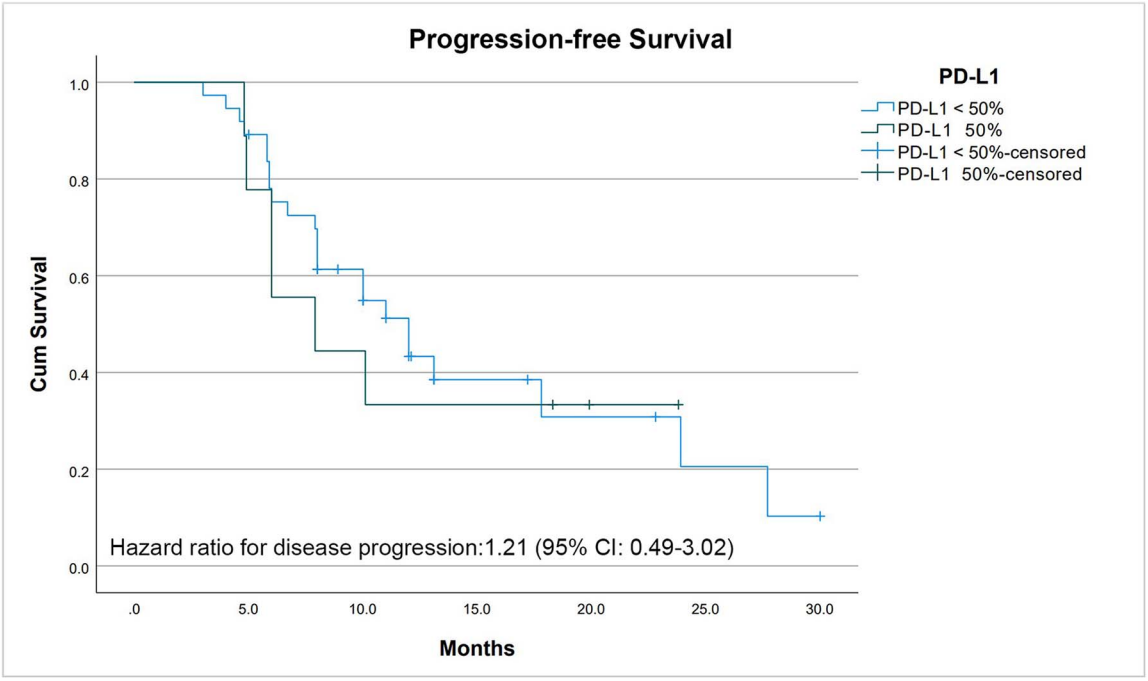

Figure 4. The progression-free survival time according to PD-L1 expression level.

Cum: cumulative; PD-L1: Programmed death ligand-1.

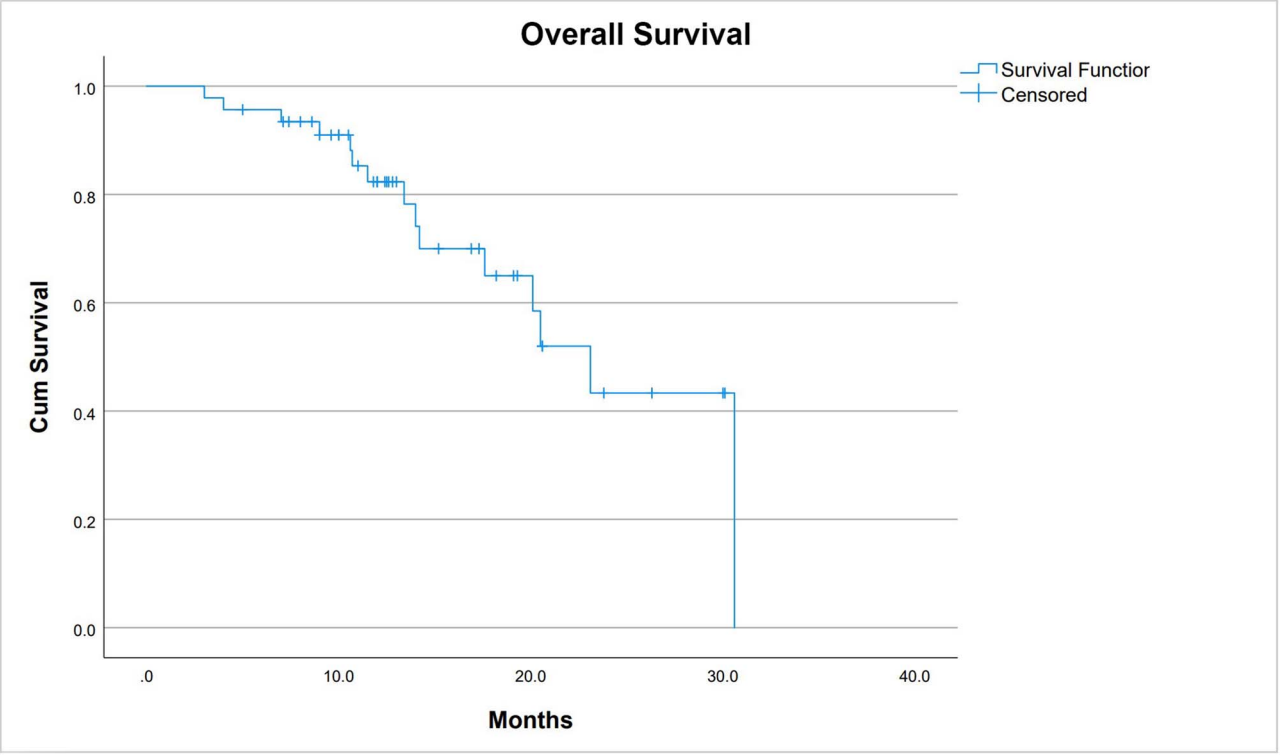

Figure 5. Overall survival.

Cum: cumulative.

was 8.0 months ($n = 25$, 95% CI, 6.4–9.6 months). This difference is statistically significant ($p < 0.05$). Currently, there is no head-to-head study between these two regimens, so future studies are needed to evaluate this issue more thoroughly.

The results of our study show that patients with NSCLC without brain metastases have a longer PFS time than patients with brain metastases (12 and 10 months, respectively). Still, the difference between the two groups was not statistically significant. A meta-analysis by Powell et al[15] of 171 patients with NSCLC and brain metastases treated with pembrolizumab in combination with platinum-doublet from three studies KEYNOTE-021, -189, and -407, indicating PFS of 6.9 months.

In the study, OS was 23.1 months (Fig. 5), which is greater than that of the KEYNOTE-407 in the group of patients treated with pembrolizumab in combination with chemotherapy, achieving an OS of 17.1 months, and in the placebo group combined with chemotherapy, accounting for 11.6 months.[16] A 1-year OS rate reached 82.3%, approximately equivalent to the study of Horinouchi et al,[14] in which an estimated 1-year OS rate was achieved in 92% of 25 patients treated with pembrolizumab in combination with pemetrexed and platinum. Among the seven patients who died in the first year, two had severe disease progression and died after three or four cycles of immunotherapy combined with chemotherapy. A 2-year OS rate accounted for 43.3%, which was higher than that of the study by Cheng et al[13], which included 65 Chinese patients with NSCLC treated with pembrolizumab in combination with chemotherapy, and 2-year OS was only 24.2%.

Side effects in the hematopoietic system were mainly anemia, mostly in the mild stage. However, two patients (4.3%) with severe anemia received red blood cell transfusions. This rate was equal to the study of Cheng et al,[13] with 4.6% of patients with anemia grades 3–5. There are 8.6% of patients with severe neutropenia. About half of the patients who had problems with elevated liver enzymes

Table 2. Side effects

Side Effects	Grade 1 or 2, *n* (%)	Grade 3 or 4, *n* (%)
Anemia	38 (82.6)	2 (4.3)
Neutropenia	16 (34.7)	4 (8.6)
Thrombocytopenia	10 (21.7)	1 (2.1)
Elevated liver enzymes	23 (40)	2 (4.3)
Elevated creatinine	5 (10.9)	0 (0)
Tired	24 (52.2)	2 (4.3)
Nausea or vomiting	14 (30.4)	1 (2.1)
Decreased appetite	19 (41.3)	1 (2.1)
Diarrhea	5 (10.9)	0 (0)
Constipation	2 (4.3)	0 (0)
Alopecia	32 (69.6)	9 (19.6)
Fever	5 (10.9)	0 (0)
Dermatitis and paronychia	5 (10.9)	0 (0)
Interstitial pneumonia	4 (8.6)	1 (2.1)
Hypothyroidism	2 (4.3)	0 (0)
Colitis	2 (4.3)	0 (0)
Myositis	8 (17.4)	1 (2.1)
Nephritis	1 (2.1)	0 (0)

during treatment, including one patient with grade 2 hepatitis due to immunotherapy, were treated with corticosteroids but did not respond; as a result, the patient permanently discontinued immunotherapy and was maintained on pemetrexed. One patient with grade 1 interstitial pneumonia continued to receive immunotherapy; two patients with grade 2 interstitial pneumonia and one with grade 3 interstitial pneumonia were delayed in receiving immunotherapy and switched to corticosteroid therapy.

Besides the obtained results, our study also has certain limitations, such as small sample size, the retrospective design of the study, short follow-up time, and no control group (chemotherapy alone or combination chemotherapy with placebo); therefore, do not highlight the value of pembrolizumab-containing regimens in improving OS and PFS.

CONCLUSION

Treatment of stage IV NSCLC without *EGFR* and *ALK* gene mutations with the immunotherapy protocol of pembrolizumab in combination with platinum-based doublet chemotherapy resulted in favorable outcomes without any new safety concerns. Future studies should include a larger sample size and longer follow-up.

Acknowledgments

The authors thank colleagues in four hospitals for their support in collecting data.

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