Original Article

Comparison of camrelizumab, pembrolizumab, tislelizumab, and sintilimab as first-line treatment in patients with non-small cell lung cancer: a retrospective study

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Background: Immune checkpoint inhibitors (ICIs) have significantly altered the first-line treatment paradigm for non-small cell lung cancer (NSCLC) without driver gene alterations. The efficacy and safety of different programmed cell death protein-1 (PD-1) inhibitors in the treatment of advanced NSCLC in Chinese real-world clinical practice remain unclear. This study aimed to analyze the efficacy and safety of camrelizumab, pembrolizumab, tislelizumab, and sintilimab retrospectively as first-line treatment options for advanced NSCLC in Chinese real-world applications.

Methods: A total of 452 NSCLC patients treated with camrelizumab, pembrolizumab, tislelizumab, or sintilimab as first-line treatment between January 2019 and June 2023 in Jiangsu Cancer Hospital were retrospectively evaluated. Adverse events and patient responses were assessed using Common Terminology Criteria for Adverse Events v5.0 and Response Evaluation Criteria for Solid Tumors v1.1. The progression-free survival (PFS) was estimated using the Kaplan-Meier method or Cox survival regression model and compared using the log-rank test.

Results: There were no significant differences in objective response rate (ORR) and median progression-free survival (mPFS) among the camrelizumab, pembrolizumab, tislelizumab, and sintilimab groups (ORR: 43.0% *vs.* 40.5% *vs.* 49.3% *vs.* 51.0%, P=0.33; mPFS: 8.51 *vs.* 10.97 *vs.* 9.43 *vs.* 9.79 months, P=0.31). Similar incidences of immune-related adverse events (irAEs) at any grade were observed in different PD-1 inhibitors (P=0.21). Similarly, no statistically significant differences in the incidence of grade 3 and 4 irAEs were observed (P=0.63). The Cox proportional hazard modeling analysis suggested that physical performance, occurrence of irAEs were all connected with the prognosis. The type of PD-1 inhibitors was not an independent prognostic factor affecting PFS.

Conclusions: Camrelizumab, pembrolizumab, tislelizumab, and sintilimab possess similar efficacy as first-line treatment options for patients with advanced NSCLC in Chinese clinical practice. Any grade or grade ≥3 irAEs are comparable between the four PD-1 inhibitors.

Keywords: Non-small cell lung cancer (NSCLC); camrelizumab; pembrolizumab; tislelizumab; sintilimab

Submitted Sep 08, 2024. Accepted for publication Dec 20, 2024. Published online Feb 13, 2025.
doi: 10.21037/jtd-24-1495
View this article at: https://dx.doi.org/10.21037/jtd-24-1495

Introduction

Data published by the American Cancer Society in 2023 showed that lung cancer is the leading cause of cancer-related deaths worldwide (1). In recent years, immune checkpoint inhibitors (ICIs) have completely changed the treatment scenario and demonstrated a remarkable efficacy in non-small cell lung cancer (NSCLC). Currently, three types of ICIs are approved by the U.S. Food and Drug Administration: a monoclonal antibody targeting the coinhibitory protein cytotoxic T lymphocyte-associated protein 4 (2), antibodies targeting the programmed cell death protein-1 (PD-1) and its ligand, programmed cell death ligand 1 (PD-L1).

PD-1 inhibitors are a type of anticancer drugs that send inhibitory signals to activated T cells by binding to PD-1 ligands PD-L1 and PD-L2, which are found on antigen-presenting cells (3). The KEYNOTE-024 Phase III clinical trial found that, for patients with NSCLC and PD-L1 expression present in 50% or more of their tumor cells, pembrolizumab monotherapy led to a notable improvement in both progression-free survival (PFS) and overall survival (OS), significantly outperforming platinum-based chemotherapy (4). Subsequently, the KEYNOTE-042 study revealed that the OS of NSCLC patients positive for PD-L1 (with ≥1% expression) treated with pembrolizumab alone as initial therapy was significantly prolonged compared to those who received platinum-based chemotherapy (5). Following the positive outcomes of these studies, both the China National Medical Products Administration and the U.S. Food and Drug Administration have granted approval for pembrolizumab monotherapy as a first-line treatment option for patients with advanced NSCLC exhibiting positive PD-L1 expression.

The durable safety and efficacy of various PD-1 inhibitors in combination with chemotherapy as first-line therapy for advanced NSCLC lacking driver mutations have been proven in numerous large randomized clinical trials. In the KEYNOTE-407 trial, pembrolizumab in combination with carboplatin and paclitaxel/nab-paclitaxel exhibited substantially extended OS and PFS compared to placebo plus chemotherapy as first-line treatment for advanced squamous NSCLC (6). Furthermore, the 5-year outcomes from the KEYNOTE-189 Phase III clinical study indicated that first-line pembrolizumab combined with pemetrexed-platinum significantly enhanced OS and PFS compared to placebo plus chemotherapy for advanced non-squamous NSCLC (7). Domestic PD-1 inhibitors combined with chemotherapy such as camrelizumab (8,9), tislelizumab (10,11), and sintilimab (12,13) have also been proven effective as first-line treatment for advanced NSCLC patients in several large clinical trials. Due to their favorable efficacy and manageable safety profiles, the combination chemotherapy of camrelizumab, pembrolizumab, tislelizumab, and sintilimab have been approved as first-line treatment options for driver-negative NSCLC in China, providing physicians with multiple options.

However, because existing trials mostly used chemotherapy drugs as placebos, a direct comparative study performed on the detection of efficacy and safety of different PD-1 inhibitors in advanced NSCLC is lacking. In addition, PD-1 inhibitors developed by different manufacturers vary in drug composition, pharmacokinetics, pharmacodynamics, and affinities to PD-1, which may lead to differences in efficacy and safety. Pembrolizumab Fab utilizes its complementary decision and framework regions to interact with the C'D loop of human PD-1, whereas sintilimab interacts with the FG loop (14,15). Compared with other PD-1 inhibitors, tislelizumab uses an IgG4 variant to optimize the antibody subtype instead of the commonly used IgG4S228P (16). However, the extent to which differences in drug structure, binding sites, and affinity affect the efficacy of PD-1

Highlight box

Key findings

- Camrelizumab, pembrolizumab, tislelizumab, and sintilimab possess similar efficacy and moderate adverse effects as first-line treatment options for patients with advanced non-small cell lung cancer (NSCLC) in Chinese real-world clinical practice.

What is known and what is new?

- The use of immune checkpoint inhibitors has revolutionized the treatment of NSCLC without driver gene alterations, achieved high response rates as first-line treatment. The optimal choice of programmed cell death protein-1 (PD-1) inhibitors for first-line treatment remains unclear.
- In our study, there were no significant differences in objective response rate and median progression-free survival (PFS) among the camrelizumab, pembrolizumab, tislelizumab, and sintilimab groups. Similar incidences of immune-related adverse events (irAEs) at any grade or grade ≥3 irAEs were observed in different PD-1 inhibitors. In multivariate analysis, the type of PD-1 inhibitors was not an independent prognostic factor affecting PFS.

What is the implication, and what should change now?

- Further studies are warranted to examine the efficacy and safety of different PD-1 inhibitors as first-line treatment options in large randomized prospective cohorts.

inhibitors is unclear. The CTONG1901 study was an open-label, randomized, Phase II clinical study that directly compared the efficacy and safety of sintilimab with those of pembrolizumab in the first-line treatment of advanced NSCLC. The results showed no difference in the efficacy between sintilimab and pembrolizumab, either as ICI monotherapy or in combination with chemotherapy (17). Future studies should focus on finding a better type of ICI inhibitor drug.

This study aimed to analyze the efficacy and safety of camrelizumab, pembrolizumab, tislelizumab, and sintilimab retrospectively as first-line treatment options for advanced NSCLC in Chinese real-world applications, helping clinicians select the best drug for each patient. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-1495/rc).

Methods

Study population

Between January 2019 and June 2023, patients who were histologically or clinically diagnosed with NSCLC and treated with ICI monotherapy or combined therapy with other regimens at Jiangsu Cancer Hospital were retrospectively enrolled. The last follow-up and data collection were conducted in November 2023. The inclusion criteria were as follows: (I) patients aged 18–80 years; (II) patients with Eastern Cooperative Oncology Group performance status (ECOG PS) ≤2; (III) patients with histologically or cytologically confirmed Stage IV NSCLC and without driver gene alternations; (IV) patients who had received ICI monotherapy or ICI therapy combined with chemotherapy/anti-angiotherapy as first-line treatment; (V) patients with complete clinicopathological data for evaluation; and (VI) patients who had undergone the required imaging examination before and after treatment. The exclusion criteria were as follows: (I) patients without measurable diseases; (II) patients with other concurrent malignancy; (III) patients who had received previous systemic therapy; and (IV) patients who shifted to use another ICI without progression disease during treatment. The anti-PD-1 drugs used in the study were pembrolizumab, camrelizumab, tislelizumab, and sintilimab. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Academic Ethics Committee of Jiangsu Cancer Hospital [No. (2024)068], and informed consent was waived because of the retrospective nature of the analysis.

Data collection and response assessment

The essential clinical characteristics extracted from the enrolled studies included gender, age, ECOG PS, pathological types, treatment regimen options, type of PD-1 inhibitors, PD-L1 expression, initiation time of ICI therapy, combination chemotherapy, combination anti-vascular drugs, optimal efficacy, and adverse effects. Data and follow-up records were updated as of November 2023. Tumor response to immunotherapy was assessed using the Response Evaluation Criteria in Solid Tumors 1.1. The indicators included complete response (CR), partial response (PR), and stable disease (SD), which were achieved at least once during the therapy. The objective response rate (ORR) was defined as the proportion of patients with the best overall response of CR or PR. The disease control rate (DCR) was defined as the proportion of patients with the best overall response of CR, PR, or SD. PFS was defined as the time from the first use of PD-1 inhibitors to disease progression or death. Adverse events (AEs) were recorded and graded for severity by using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0. Immune-related adverse events (irAEs) were defined as AEs that occurred or worsened on or after ICIs treatment initiation.

Statistical analysis

Comparisons between distinct groups were analyzed using Chi-squared or Fisher's exact test for categorical variables. Kaplan-Meier PFS curves were plotted using GraphPad Prism 9.5 software and compared using a log-rank test. Hazard ratios (HRs) and two-sided 95% confidence intervals (CIs) were calculated by using the Cox proportional-hazard model. A two-tailed P value of ≤0.05 was statistically significant. Statistical analyses were performed using SPSS version 26.0 (SPSS, Inc.).

Results

Patient characteristics

A total of 452 patients were enrolled in this study. Baseline demographics and disease characteristics for the patients

Table 1 Clinical characteristics of patients and clinical activity of first-line treatment (n=452)

Characteristics	All (n=452), n (%)	Camrelizumab (n=93), n (%)	Pembrolizumab (n=121), n (%)	Tislelizumab (n=140), n (%)	Sintilimab (n=98), n (%)
Sex					
Female	82 (18.1)	18 (19.4)	23 (19.0)	20 (14.3)	21 (21.4)
Male	370 (81.9)	75 (80.6)	98 (81.0)	120 (85.7)	77 (78.6)
Age (years)					
≤60	145 (32.1)	37 (39.8)	42 (34.7)	35 (25.0)	31 (31.6)
>60	307 (67.9)	56 (60.2)	79 (65.3)	105 (75.0)	67 (68.4)
Pathologic type					
Non-squamous carcinoma	260 (57.5)	69 (74.2)	81 (66.9)	49 (35.0)	61 (62.2)
Squamous carcinoma	192 (42.5)	24 (25.8)	40 (33.1)	91 (65.0)	37 (37.8)
PD-L1 expression					
<1%	40 (8.8)	9 (9.7)	18 (14.9)	3 (2.1)	10 (10.2)
1% to 49%	78 (17.3)	27 (29.0)	22 (18.2)	17 (12.1)	12 (12.2)
≥50%	62 (13.7)	12 (12.9)	28 (23.1)	11 (7.9)	11 (11.2)
Missing	272 (60.2)	45 (48.4)	53 (43.8)	109 (77.9)	65 (66.3)
ECOG PS					
0	131 (29.0)	14 (15.1)	38 (31.4)	51 (36.4)	28 (28.6)
1	276 (61.1)	70 (75.3)	74 (61.2)	74 (52.9)	58 (59.2)
2	45 (10.0)	9 (9.7)	9 (7.4)	15 (10.7)	12 (12.2)
First-line treatment received					
ICI monotherapy	10 (2.2)	0 (0.0)	3 (2.5)	5 (3.6)	2 (2.0)
ICIs + chemotherapy	351 (77.7)	64 (68.8)	96 (79.3)	115 (82.1)	76 (77.6)
ICIs + chemotherapy + antiangiogenic drugs	71 (15.7)	26 (28.0)	15 (12.4)	13 (9.3)	17 (17.3)
ICIs + antiangiogenic drugs	20 (4.4)	3 (3.2)	7 (5.8)	7 (5.0)	3 (3.1)

PD-L1, programmed cell death ligand 1; ECOG PS, Eastern Cooperative Oncology Group performance status; ICI, immune checkpoint inhibitor.

included are shown in *Table 1*. The median age of the patients was 65 years, and the sample included 370 males and 82 females. The majority of patients (57.5%, 260/452) were diagnosed with non-squamous cell carcinoma. Most (90.0%) patients had an ECOG PS of 0 or 1. All patients received PD-1 inhibitors alone or in combination with chemotherapy and/or anti-angiogenic drugs as the first-line treatment. Based on the type of PD-1 inhibitors treatment they received, patients were divided into four groups: the camrelizumab group (93 cases), the pembrolizumab group (121 cases), the tislelizumab group (140 cases), and the sintilimab group (98 cases). A total of 180 patients had known PD-L1 expression before treatment. In terms of PD-L1 expression level, 62 cases (13.7%) were ≥50%, 78 cases (17.3%) were 1–49%, and 40 cases (8.8%) were <1%.

Assessment of efficacy

Imaging data were available for 452 patients for specific efficacy assessment, with 5 patients achieving CR and 203 patients achieving PR, for an overall ORR of 46.0% and an overall DCR of 90.5%. All the patients who achieved

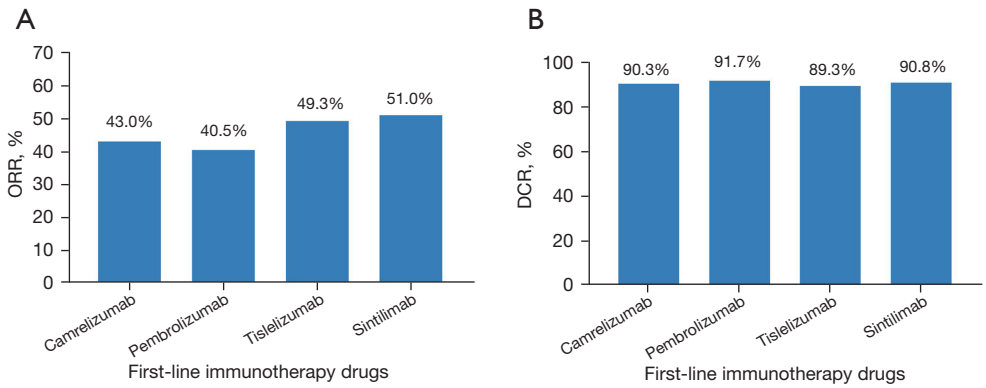

Figure 1 Clinical outcomes of the first-line treatment. (A) ORR of patients with different PD-1 inhibitor options. (B) DCR of patients with different PD-1 inhibitor options. ORR, objective response rate; PD-1, programmed cell death protein-1; DCR, disease control rate.

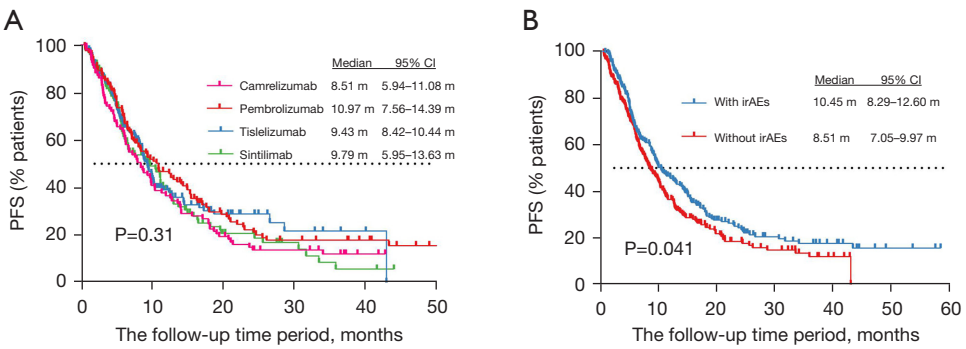

Figure 2 Kaplan-Meier curves of the first-line treatment. (A) PFS of patients with different PD-1 inhibitor options. (B) PFS of patients with or without irAEs. PFS, progression-free survival; PD-1, programmed cell death protein-1; irAEs, immune-related adverse events.

a CR were treated with combination regimen treatment. Patients with better ECOG PS had higher ORR and DCR than those with poorer performance status (ORR: 56.5% *vs.* 43.8% *vs.* 28.9%, P=0.003; DCR: 93.9% *vs.* 91.3% *vs.* 75.6%, P=0.003). ORR for the first-line treatment was numerically higher in the sintilimab group (51.0%, P=0.33) and DCR was the highest in the pembrolizumab group (91.7%, P=0.93) (*Figure 1*).

The median PFS (mPFS) was 9.46 months in all patients (95% CI: 8.49–10.43 months), with a mPFS of 8.51 months (95% CI: 5.94–11.08 months) in the camrelizumab group, 10.97 months (95% CI: 7.56–14.39 months) in the pembrolizumab group, 9.43 months (95% CI: 8.42–10.44 months) in the tislelizumab group, 9.79 months (95% CI: 5.95–13.63 months) in the sintilimab group. The pembrolizumab group tended to achieve longer PFS, although these four groups were without statistically significant differences (P=0.31) (*Figure 2A*).

The mPFS was 14.19 months with 95% CI of 9.86–18.53 months of PD-L1 expression level ≥50% group, followed by patients with low PD-L1 (mPFS: 9.46 months, 95% CI: 7.70–11.22), followed by PD-L1 with unknown expression patients (mPFS: 9.36 months, 95% CI: 7.95–10.77), and PD-L1 negative patients achieved the lowest PFS (6.21 months, 95% CI: 4.43–7.99), which was statistically significant (P=0.03).

Evaluation of efficacy in patients known PD-L1 expression before treatment (n=180)

ORR in patients with negative PD-L1 expression was similar between the different PD-1 inhibitor groups (camrelizumab *vs.* pembrolizumab *vs.* tislelizumab *vs.* sintilimab: 22.2% *vs.* 27.8% *vs.* 33.3% *vs.* 50.0%, P=0.60). In addition, ORR in patients with low or high PD-L1 expression were without statistically significant differences

Table 2 Treatment efficacy of different PD-1 inhibitors in patients known PD-L1 expression before treatment (n=180)

Best overall response	Camrelizumab	Pembrolizumab	Tislelizumab	Sintilimab	P value
PD-L1 ≥50%, n/n (%)	12	28	11	11	
CR	0	0	0	0	–
PR	6 (50.0)	14 (50.0)	7 (63.6)	9 (81.8)	–
SD	5 (41.7)	12 (42.9)	4 (36.4)	2 (18.2)	–
PD	1 (8.3)	2 (7.1)	0	0	–
ORR (%)	50.0	50.0	63.3	81.8	0.30
mPFS (months)	10.48	17.71	8.94	11.17	0.48
1%≤ PD-L1 <50%, n/n (%)	27	22	17	12	
CR	1 (3.7)	0	0	0	–
PR	11 (40.7)	8 (36.4)	7 (41.2)	8 (66.7)	–
SD	14 (51.9)	14 (63.6)	8 (47.1)	4 (33.3)	–
PD	1 (3.7)	0	2 (11.8)	0	–
ORR (%)	44.4	36.4	41.2	66.7	0.39
mPFS (months)	8.90	12.75	8.38	10.68	0.59
PD-L1 <1%, n/n (%)	9	18	3	10	
CR	0	0	0	0	–
PR	2 (22.2)	5 (27.8)	1 (33.3)	5 (50.0)	–
SD	7 (77.8)	12 (66.7)	1 (33.3)	4 (40.0)	–
PD	0	1 (5.6)	1 (33.3)	1 (10.0)	–
ORR (%)	22.2	27.8	33.3	50.0	0.60
mPFS (months)	3.02	6.21	5.82	8.94	0.44

PD-1, programmed cell death protein-1; PD-L1, programmed cell death ligand 1; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; mPFS, median progression-free survival.

(low PD-L1 expression group, high PD-L1 expression group: camrelizumab *vs.* pembrolizumab *vs.* tislelizumab *vs.* sintilimab: 44.4% *vs.* 36.4% *vs.* 41.2% *vs.* 66.7%, P=0.39; 50.0% *vs.* 50.0% *vs.* 63.3% *vs.* 81.8%, P=0.30) (*Table 2*).

Among those 40 patients with negative PD-L1 expression, the mPFS was 3.02 months of camrelizumab group, 6.21 months of pembrolizumab group, 5.82 months of tislelizumab group, and 8.94 months of sintilimab group (P=0.44). Among those 78 patients with low PD-L1 expression, the mPFS was 8.90 months for the camrelizumab group, 12.75 months for the pembrolizumab group, 8.38 months for the tislelizumab group, and 10.68 months for the sintilimab group (P=0.59). Among those 62 patients with high PD-L1 expression, the mPFS was 10.48 months for the camrelizumab group, 17.71 months for the pembrolizumab group, 8.94 months for the tislelizumab group, and 11.17 months for the sintilimab group (P=0.48) (*Table 2*).

Prognostic factors for PFS

Multivariate Cox regression analysis of all patients (n=452), including sex, age, histology, ECOG PS score, combination of therapeutic regimen, type of PD-1 inhibitors, and occurrence or non-occurrence of irAEs, further confirmed that physical performance, occurrence of irAEs were all connected with the prognosis. The type of PD-1 inhibitors was not an independent prognostic factor affecting PFS (*Table 3*). As shown in *Table 4*, multivariate analysis of patients known PD-L1 expression before treatment (n=180)

Table 3 Univariate analysis and multivariate analysis of factors of progression-free survival in all patients (n=452)

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Male *vs.* female	1.171 (0.883–1.553)	0.27	–	–
Age >60 *vs.* ≤60 years	0.823 (0.658–1.029)	0.09	–	–
Non-squamous carcinoma *vs.* squamous carcinoma	0.837 (0.676–1.038)	0.11	–	–
Combination therapy *vs.* monotherpay	2.383 (0.889–6.389)	0.08	–	–
ECOG PS				
0	Reference		Reference	
1	1.340 (1.043–1.722)	0.02	1.400 (1.087–1.804)	0.009
2	2.172 (1.495–3.157)	<0.001	2.251 (1.548–3.273)	<0.001
With irAEs *vs.* without irAEs	0.800 (0.646–0.991)	0.041	0.763 (0.615–0.947)	0.01
Type of PD-1 inhibitors				
Camrelizumab	Reference		–	–
Pembrolizumab	0.781 (0.580–1.052)	0.10	–	–
Tislelizumab	0.812 (0.602–1.095)	0.17	–	–
Sintilimab	0.943 (0.689–1.290)	0.71	–	–

HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; irAEs, immune-related adverse events; PD-1, programmed cell death protein-1.

showed that physical performance, occurrence of irAEs, and PD-L1 expression level were associated with PFS.

Safety

Table 5 shows that 45.1% (204/452) of patients experienced irAEs in the first-line treatment. Several (9.5%, 43/452) patients experienced grade 3 or 4 AEs. The condition improved slowly after stopping medication and systemic steroids. No deaths due to fatal irAEs were reported. The most commonly reported irAEs were hypothyroidism (10.4%, 47/452), reactive cutaneous capillary endothelial proliferation (RCCEP) (10.2%, 46/452), pneumonia (8.2%, 37/452), and rash (8.0%, 36/452). Other common irAEs included pruritus, hyperthyroidism, increased creatinine, myocarditis, colitis, increased alanine aminotransferase/aspartate transaminase (ALT/AST), paresthesia, and oral ulcer.

The mPFS was 10.45 months with 95% CI of 8.29–12.60 months for patients with irAEs and 8.51 months with 95% CI of 7.05–9.97 months for patients without irAEs, which was a statistically significant difference (P=0.041) (*Figure 2B*). In addition, one patient achieved CR and 104 patients achieved PR as the best response in irAEs group; four patients achieved CR and 99 patients achieved PR as the best response in patients without irAEs. The ORR in the irAE group was significantly higher than in patients without irAE group (51.5% *vs.* 41.5%, P=0.04).

RCCEP occurred only in patients treated with camrelizumab. The numbers of patients with irAEs were 51 (54.8%), 53 (43.8%), 59 (42.1%), and 41 (41.8%) in the camrelizumab, pembrolizumab, tislelizumab, and sintilimab groups, respectively, whereas the incidences of grade 3 or 4 irAEs in the same groups were 11 (11.8%), 13 (10.7%), 10 (7.1%), and 9 (9.2%), respectively. Similar incidences of irAEs at any grade were observed in different PD-1 inhibitors groups (P=0.21). Similarly, no statistically significant differences in the incidence of grade 3 and 4 irAEs were observed (P=0.63).

Discussion

In this real-world study, the efficacy and safety of different PD-1 inhibitors as first-line treatment for advanced NSCLC were explored. No statistical difference was observed in the comparison of efficacy among the agents

Table 4 Univariate analysis and multivariate analysis of factors of progression-free survival in patients known PD-L1 expression before treatment (n=180)

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Male *vs.* female	1.217 (0.805–1.841)	0.35	–	–
Age >60 *vs.* ≤60 years	0.778 (0.555–1.091)	0.15	–	–
Non-squamous carcinoma *vs.* squamous carcinoma	0.874 (0.608–1.257)	0.47	–	–
ECOG PS				
0	Reference		Reference	
1	1.815 (1.158–2.845)	0.009	2.118 (1.324–3.389)	0.002
2	2.511 (1.321–4.772)	0.005	2.914 (1.516–5.600)	0.001
With irAEs *vs.* without irAEs	0.693 (0.497–0.965)	0.03	0.547 (0.383–0.781)	0.001
Type of PD-1 inhibitors				
Camrelizumab	Reference		–	–
Pembrolizumab	0.640 (0.424–0.965)	0.03	–	–
Tislelizumab	0.931 (0.556–1.558)	0.79	–	–
Sintilimab	0.832 (0.519–1.334)	0.45	–	–
PD-L1 expression level				
PD-L1 ≥50%	Reference		–	–
1%≤ PD-L1 <50%	1.550 (1.046–2.298)	0.03	1.448 (0.975–2.150)	0.047
PD-L1 <1%	1.945 (1.239–3.054)	0.004	2.007 (1.269–3.173)	0.003

PD-L1, programmed cell death ligand 1; HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; irAEs, immune-related adverse events; PD-1, programmed cell death protein-1.

camrelizumab, pembrolizumab, tislelizumab, and sintilimab as first-line treatment in patients with NSCLC. In addition, all irAEs associated with the four PD-1 inhibitors were manageable. This study is important for clinicians and patients to decide when faced with multiple PD-1 inhibitor drug options.

In clinical trials, ICIs have achieved significant clinical efficacy, and higher ORR and longer PFS and OS than chemotherapy. However, no authoritative guidelines are available on the preferred use of different PD-1 inhibitors in the first-line treatment of patients with advanced NSCLC. In our study, the response data among the camrelizumab, pembrolizumab, tislelizumab, and sintilimab groups were similar (ORR: 43.0% *vs.* 40.5% *vs.* 49.3% *vs.* 51.0%, P=0.33). The mPFS among the camrelizumab, pembrolizumab, tislelizumab, and sintilimab groups were also similar (mPFS: 8.51 *vs.* 10.97 *vs.* 9.43 *vs.* 9.79 months, P=0.31). The mPFS in the pembrolizumab group was numerically the longest (mPFS =10.97 months), whereas that of the sintilimab group was higher in terms of ORR (ORR =51.0%); none of the differences were statistically significant. Compared with the mPFS reported in KEYNOTE-189, KEYNOTE-407, ORIENT-11, and ORIENT-12 clinical trials, our study obtained a better efficacy (6,7,12,13). Several reasons may account for the results. First, the dissimilarities in baseline patient characteristics may vary from those in clinical trials. Second, the treatment strategies in daily practice are not identical to those in clinical trials. For example, the patients enrolled in our study also included patients who were treated with anti-angiogenic drugs in combination with ICI therapy. The findings of the IMpower150 study suggested that the efficacy of a combination of bevacizumab, atezolizumab, carboplatin, and paclitaxel could result in significant enhancements in PFS and OS in patients with metastatic NSCLC, which may affect the outcomes of our study (18).

Table 5 Immune-related adverse events of all patients (n=452)

Events	Grade	Camrelizumab (n=93), n (%)	Pembrolizumab (n=121), n (%)	Tislelizumab (n=140), n (%)	Sintilimab (n=98), n (%)	P
Pruritus	Any grade	3 (3.2)	5 (4.1)	5 (3.6)	4 (4.1)	0.98
	Grade 3–5	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0.42
Rash	Any grade	8 (8.6)	13 (10.7)	7 (5.0)	8 (8.2)	0.39
	Grade 3–5	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0.42
RCCEP	Any grade	46 (49.5)	0 (0.0)	0 (0.0)	0 (0.0)	<0.001
	Grade 3–5	13 (14.0)	0 (0.0)	0 (0.0)	0 (0.0)	<0.001
Hyperthyroidism	Any grade	2 (2.2)	4 (3.3)	5 (3.6)	2 (2.0)	0.89
	Grade 3–5	0 (0.0)	1 (0.8)	1 (0.7)	0 (0.0)	>0.99
Hypothyroidism	Any grade	14 (15.1)	15 (12.4)	10 (7.1)	8 (8.2)	0.18
	Grade 3–5	2 (2.2)	1 (0.8)	0 (0.0)	1 (1.0)	0.31
Pneumonia	Any grade	3 (3.2)	12 (9.9)	13 (9.3)	9 (9.2)	0.27
	Grade 3–5	0 (0.0)	2 (1.7)	4 (2.9)	1 (1.0)	0.44
Elevated ALT/AST	Any grade	4 (4.3)	3 (2.5)	8 (5.7)	2 (2.0)	0.43
	Grade 3–5	0 (0.0)	1 (0.8)	2 (1.4)	0 (0.0)	0.71
Creatinine increased	Any grade	7 (7.5)	8 (6.6)	4 (2.9)	6 (6.1)	0.40
	Grade 3–5	2 (2.2)	1 (0.8)	0 (0.0)	1 (1.0)	0.31
Colitis	Any grade	3 (3.2)	6 (5.0)	5 (3.6)	3 (3.1)	0.91
	Grade 3–5	1 (1.1)	1 (0.8)	0 (0.0)	0 (0.0)	0.46
Paresthesia	Any grade	1 (1.1)	0 (0.0)	1 (0.7)	1 (1.0)	0.79
	Grade 3–5	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	>0.99
Oral ulcer	Any grade	3 (3.2)	0 (0.0)	2 (1.4)	2 (2.0)	0.23
	Grade 3–5	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	>0.99
Myocarditis	Any grade	2 (2.2)	4 (3.3)	3 (2.1)	2 (2.0)	0.93
	Grade 3–5	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	0.69

RCCEP, reactive cutaneous capillary endothelial proliferation; ALT, alanine aminotransferase; AST, aspartate transaminase.

The CTONG1901 study was the first open-label, randomized, Phase II clinical trial that directly compared the effectiveness and safety of sintilimab versus pembrolizumab in the initial treatment of advanced NSCLC. The study revealed no significant difference in PFS or OS between the two drugs, whether as ICI monotherapy (mPFS: 7.6 *vs.* 11.0 months, P=0.57; OS: 14.9 *vs.* 22.6 months, P=0.64) or in combination therapies (mPFS: 7.4 *vs.* 7.1 months, P=0.98; OS: 14.7 *vs.* 17.3 months, P=0.59) (17). One real-world retrospective study had shown similar efficacy and toxicity between pembrolizumab and sintilimab in the first-line treatment of advanced NSCLC patients (19). Compared with this retrospective study of comparing sintilimab and pembrolizumab mentioned above, our study, which encompassed a larger sample and more types of PD-1 inhibitors, likewise found no noteworthy distinctions in ORR and PFS among different PD-1 inhibitors for first-line treatment in advanced NSCLC. Another retrospective study on 351 NSCLC patients treated with ICIs compared more ICIs and similarly observed no statistically significant differences in effectiveness and safety among different ICIs (20).

PD-L1 expression is commonly measured by the tumor proportion score (TPS). Study has shown more favorable clinical responses in patients with PD-L1-positive cancer, which is also depicted by promising objective responses (21). The potential of PD-L1 expression status as a biomarker to guide molecular selection for advanced NSCLC was also explored in our study. In our study, patients with high PD-L1 expression had the highest ORR and longest PFS, and the differences were all statistically significant. Multivariate analysis of patients known PD-L1 expression before treatment (n=180) also showed that PD-L1 expression level was an independent prognostic factor affecting PFS (*Table 4*). The mPFS was numerically highest with pembrolizumab than with three other agents (mPFS =10.97 months). In patients who received a PD-L1 expression assay before pembrolizumab therapy, 23.1% (28/121) had high PD-L1 expression, which exceeded the proportions in the three other PD-1 inhibitor groups. The KEYNOTE-024 study showed excellent efficacy of the pembrolizumab monotherapy group in patients with PD-L1 ≥50% (4), but key issues arise. First, in clinical practice, the PD-L1 test is not reimbursed by Medicare, and the test does not cover all populations due to its high price. Second, real-world PD-L1 immunohistochemistry (IHC) assays of evaluation for PD-L1 protein level detection may differ from the use of the PD-L1 immunohistochemistry 22C3 pharmDx assay in clinical studies of pembrolizumab, which may introduce a potential bias (22). In our study, the pathologic type of patients treated with camrelizumab, pembrolizumab, or sintilimab were mostly non-squamous carcinoma, while 61% of patients in the tislelizumab group were squamous carcinoma. The reason for this result may be due to the inevitable selection bias in this study. The result of the RATIONALE 304 study indicated that tislelizumab in combination with chemotherapy showed a significant PFS benefit in advanced non-squamous NSCLC patients with PD-L1 expression greater than or equal to 50%, whereas the benefit was not significant in other PD-L1 expression groups (10). In contrast, the RATIONALE-307 study indicated that the combination of tislelizumab and chemotherapy was associated with a significantly improved efficacy and a manageable safety in patients with advanced squamous NSCLC, regardless of PD-L1 expression (11). Therefore, in the clinical data collected from patients treated in our institution, tislelizumab is more often used in the treatment of patients with advanced squamous NSCLC.

In our study, among patients with negative PD-L1 expression, ORR and mPFS were similar between the different PD-1 inhibitor groups (P=0.60; P=0.44). In addition, the ORR and PFS in the low PD-L1 expression group (P=0.39; P=0.59) and the high PD-L1 expression group (P=0.30; P=0.48) were similar between the different PD-1 inhibitor groups. In conclusion, the results of our analysis did not show any significant differences in the efficacy between these four anti-PD-1 inhibitors, even considering the PD-L1 expression. However, because the number of patients known PD-L1 expression before treatment in our study was small and not representative of the entire population, there is still an urgent need to conduct more randomized prospective trials or retrospective studies with larger samples to confirm whether these four PD-1 inhibitors have different efficacies at different PD-L1 expression levels. In addition, other biomarkers that can serve as predictors of immunotherapy efficacy remain in great demand for improved clinical decision making.

Although ICIs offer clinical benefits to patients with advanced NSCLC by activating T cells and enhancing their anti-tumoral activity, they are commonly associated with a broad spectrum of irAEs (22). These irAEs arise due to the nonspecific immunologic activations of ICIs, which can trigger autoimmune-like or inflammatory diseases and usually affect multiple organs (23). A positive correlation between the development of irAEs and immunotherapy efficacy has been reported (24). The outcomes of our study revealed that ORR was significantly higher in patients with irAEs (51.5% *vs.* 41.5%, P=0.04), as well as statistical advantages on PFS (10.45 *vs.* 8.51 months, HR =0.800; 95% CI: 0.646–0.991; P=0.041) compared with patients without any irAE. Multivariate Cox regression analysis also confirmed that the occurrence of irAEs was a positive prognostic factor affecting PFS (*Table 3*). The overall irAE situation is safe and controllable, and no fatal irAEs were noted. Similar incidences of irAEs at any grade were observed in different PD-1 inhibitor groups (P=0.21), and most of them were classified as grade 1 or 2 AEs. Similarly, no statistically significant differences in the incidence of grade 3 and 4 irAEs were observed (P=0.63). RCCEP occurred only in patients treated with camrelizumab, which is consistent with the findings of the CameL study (9). The most commonly reported irAEs in our study was hypothyroidism (10.4%, 47/452). Related study had suggested that thyroid AEs occur in approximately 10% of patients treated with anti-PD-1 or anti-PD-L1 monotherapy (25). Compared with patients receiving comprehensive treatments such as PD-1 inhibitors combined with chemotherapy or anti-vascular therapy were

more likely to present with thyroid AEs (26). The incidence of irAEs reported in our study is consistent with the known tolerability profile of PD-1 inhibitors in combination with chemotherapy.

PD-1 inhibitors are developed by different manufacturers, and drug prices are a common consideration for patients. Numerous studies have pointed to the favorable cost effectiveness of combining sintilimab or camrelizumab with chemotherapy compared with chemotherapy alone in NSCLC (27,28). However, a study demonstrated that pembrolizumab in combination with chemotherapy was not cost effective compared with chemotherapy alone in China, regardless of PD-L1 TPS (29). Pembrolizumab, which is expensive, is the only imported drug among these four drugs. Camrelizumab, tislelizumab, and sintilimab are domestically produced drugs that have been included in the National Drug Reimbursement List with the Chinese government as first-line treatment options for NSCLC. According to the latest price determined during the national reimbursement negotiation, the drug acquisition cost of tislelizumab has slipped to 1,253.53 Yuan/100 mg. Compared to the previous price, it has been significantly reduced, which continues to alleviate the financial burden of patients to a certain extent. In our study, no statistically significant difference was noted in the efficacy and toxicity of the four PD-1 inhibitors, and patients can select the most suitable drug according to their financial situation and local health insurance policy.

However, there are several limitations in this study. Firstly, the stratified analysis of PD-L1 expression was incompletely recorded because only a small number of patients were tested for PD-L1 expression, which may lead to analysis bias. Secondly, being a retrospective clinical study could lead to selection bias. Thirdly, the treatment regimen in our study involved four different PD-1 inhibitors, combined with various chemotherapy and/or anti-vascular drugs, which may have a confounding effect on the results. Finally, due to the limited follow-up time, obtaining and analyzing the OS data were not possible. Therefore, further studies are warranted to examine the efficacy and safety of different PD-1 inhibitors as first-line treatment options in large randomized prospective cohorts.

Conclusions

Camrelizumab, pembrolizumab, tislelizumab, and sintilimab display similar efficacies and tolerable safety profiles in patients with advanced NSCLC. Patients can select the most suitable anti-PD-1 drugs according to their tolerance to the adverse effects of different drugs, preferences, and economic situation.

Acknowledgments

None.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-1495/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-1495/dss

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-1495/prf

Funding: This work was supported by the National Natural Science Foundation of China (Nos. 82172872 and 82373292); Jiangsu Province Capability Improvement Project through Science, Technology and Education, Jiangsu Provincial Medical Innovation Center (No. CXZX202224).

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-1495/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Academic Ethics Committee of Jiangsu Cancer Hospital [No. (2024)068] and individual consent for this retrospective analysis was waived.

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Cite this article as: Yan X, Wang Y, Wu F, Zhou G, Shen J, Yu S. Comparison of camrelizumab, pembrolizumab, tislelizumab, and sintilimab as first-line treatment in patients with non-small cell lung cancer: a retrospective study. J Thorac Dis 2025;17(2):859-871. doi: 10.21037/jtd-24-1495