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Efficacy and Safety Analysis of Camrelizumab, Sintilimab, and Tislelizumab in the Treatment of NSCLC in Xuanwei, China: A Retrospective Real-World Study

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Research Article

Keywords: Xuanwei, NSCLC, PD-1 inhibitor, Clinical efficacy, Adverse drug reactions

Posted Date: July 7th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-9373929/v1

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Additional Declarations: No competing interests reported.

Abstract

Background

The lung cancer incidence in the Xuanwei region of Yunnan Province is the highest in China, characterized by region-specific features and unique mutation patterns. Immune checkpoint inhibitors have been increasingly used in Chinese non-small cell lung cancer (NSCLC) patients. However, the real-world efficacy and safety of programmed cell death protein 1 (PD-1) inhibitor in this population remain unknown. This study aimed to compare the clinical outcomes of camrelizumab, sintilimab, and tislelizumab between NSCLC patients from Xuanwei and non-Xuanwei regions using real-world data.

Methods

Clinical data of patients with NSCLC who received PD-1 inhibitors in the First and Third Affiliated Hospitals of Kunming Medical University were retrospectively collected through the Chinese Pharmacovigilance System (CHPS). The patients were divided into Xuanwei and non-Xuanwei groups, and the clinical efficacy and adverse reactions of PD-1 inhibitors between the two groups were compared.

Results

After propensity score matching, 156 NSCLC patients receiving camrelizumab, sintilimab, or tislelizumab were included, with balanced baseline characteristics ($P > 0.05$). objective response rate (ORR) was 31.50% and disease control rate (DCR) 85.04%. DCR was significantly higher in the Xuanwei group than in the non-Xuanwei group (95.59% vs. 72.88%, $P < 0.001$). particularly for camrelizumab (100% vs 58.33%, $P = 0.006$) and sintilimab (96.30% vs 75.00%, $P = 0.027$). In 127 palliative-care patients, median progression-free survival (PFS) was 27 months, with no between-group difference. Multivariate Cox analysis identified combined radiotherapy as an independent predictor of shorter PFS. Median overall survival for all 156 patients was 47 months. Adverse events occurred in 21.79% of patients, mostly grade 1–2 (grade 3–4: 1.28%), most commonly rash and hypothyroidism.

Conclusion

This study reveals that patients with NSCLC from the Xuanwei region achieved a significantly higher DCR when treated with camrelizumab or sintilimab. This finding suggests that there may be unique characteristics influencing the therapeutic efficacy of different PD-1 inhibitors in this specific patient population.

Background

Lung cancer is the most common cause of cancer-related death worldwide. According to data released by the National Cancer Center of China in the 2021 China Cancer Registry Annual Report, lung cancer ranks first in both incidence and mortality among all cancer types in China, with non-small cell lung cancer (NSCLC) accounting for approximately 85% of all lung cancer cases (1). In recent years, treatment regimens represented by programmed cell death protein 1 (PD-1) inhibitors have demonstrated significant efficacy in patients with NSCLC, offering the potential for long-term survival (2). However, traditional randomized controlled trials (RCTs) have stringent inclusion/exclusion criteria and are conducted in specific clinical settings, which may limit their generalizability to real-world practice. The real-world efficacy and safety of these treatments, especially in specific subpopulations, remain uncertain (3).

The Xuanwei region in Yunnan Province, China, has the highest incidence of lung cancer nationwide (4). Lung cancer in Xuanwei exhibits distinct regional characteristics: high incidence and mortality rates, a patient demographic predominantly characterized by younger age, non-smoking status, female gender, and a high frequency of adenocarcinoma, along with notable familial aggregation (5, 6). Studies have shown that the gene mutation spectrum and mutation patterns in NSCLC patients from Xuanwei differ significantly from those in patients from non-Xuanwei regions (7). Furthermore, research indicates that the positive expression rate of programmed death-ligand 1 (PD-L1) (PD-L1 > 1%) in this population is significantly higher than that in the broader East Asian patient population (5, 8, 9). Despite these known differences, no real-world study has yet compared the efficacy and safety of PD-1 inhibitors between NSCLC patients from the Xuanwei region and those from other regions.

Therefore, this study aims to retrospectively collect clinical data of NSCLC patients treated with camrelizumab, sintilimab, and tislelizumab from the First Affiliated Hospital and the Third Affiliated Hospital of Kunming Medical University using the Chinese Pharmacovigilance System (CHPS). Using propensity score matching (PSM), we will compare the efficacy and safety of PD-1 inhibitors between patients from Xuanwei and those from other regions, thereby providing evidence to inform real-world clinical decision-making for this unique population.

1 Methods

2. 1.1 Study Subjects and Inclusion/Exclusion Criteria

This study is a real-world retrospective analysis based on the CHPS. Approved by the institutional ethics committee of our hospital, we collected and screened data from patients with NSCLC who were treated with camrelizumab, sintilimab, and tislelizumab at the First Affiliated Hospital and the Third Affiliated Hospital of Kunming Medical University between July 2019 and November 2023. A total of 283 patients met the inclusion criteria and were ultimately enrolled in this study. Patients were categorized into the Xuanwei group or the non-Xuanwei group based on their household registration location. The last follow-up date was March 4, 2024.

Inclusion criteria for this study were as follows: (1) confirmed diagnosis of NSCLC by cytology or histology; (2) normal function of major organs; and (3) having received at least two cycles of PD-1 inhibitor therapy.Exclusion criteria included: (1) concurrent use of two or more types of immunotherapy; (2) pre-existing systemic autoimmune diseases; and (3) requirement for long-term corticosteroid therapy (within two weeks prior to enrollment).

The dosage and administration of the three PD-1 inhibitors were summarized in Table 1.

Table 1
Dosage and administration of PD-1 inhibitors

PD-1 inhibitor	Dosage and Administration
Camrelizumab	200mg q3w
Sintilimab	200mg/100mg q3w
Tislelizumab	200mg q3w
q3w: every 3 weeks, PD-1 inhibitor: Programmed cell death protein 1 inhibitor.	

1.2 Efficacy Evaluation

Treatment efficacy was assessed using the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1). Tumor responses were categorized as complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD).

Efficacy endpoints included the objective response rate (ORR) and disease control rate (DCR), calculated as follows:

ORR = (CR + PR) / (CR + PR + SD + PD) × 100%

DCR = (CR + PR + SD) / (CR + PR + SD + PD) × 100%

Survival endpoints included progression-free survival (PFS), and overall survival (OS).

1. 3 Adverse Events Assessment

Adverse drug reactions (ADRs) were graded for severity according to the Common Terminology Criteria for Adverse Events version 6.0. The diagnosis and grading of immune-related ADRs were performed following the 2021 guidelines for toxicity management related to immune checkpoint inhibitors issued by the Chinese Society of Clinical Oncology (CSCO).

1.4 Statistical Analysis

PSM was performed using R software to achieve a balanced distribution of baseline characteristics between the two groups, with a caliper width set at 0.03. All statistical analyses were conducted using

SPSS software (version 26.0). Categorical variables, including patient clinical characteristics, clinical efficacy outcomes, and ADRs, were compared between groups using the Chi-square (χ^2) test. PFS curves were generated using the Kaplan-Meier method, and differences between groups were compared with the Log-rank test. Multivariate regression analysis was performed using the Cox proportional hazards model. A two-sided P value of less than 0.05 was considered statistically significant.

The patient screening flowchart is presented in Figure 1.

2 Results

2.1 Baseline Clinical Characteristics of the 283 NSCLC Patients

A comparison of the baseline characteristics between the two groups before PSM is presented in Table 2. Prior to matching, statistically significant differences ($P < 0.05$) were observed between the two groups in terms of sex, age, presence of comorbidities, ECOG performance status, PD-L1 expression level, pathological type, and line of therapy. After PSM, 78 matched pairs (156 patients in total) were included in the final analysis. Subsequent comparison of the matched cohorts revealed no statistically significant differences in any of the baseline characteristics ($P > 0.05$, Table 3).

A comparison of the treatment regimens between the two groups is summarized in Table 4. No statistically significant differences were observed either before PSM ($P = 0.218$) or after matching ($P = 0.754$).

Table 2
Patients' baseline characteristics before PSM

Clinical Characteristics	Xuanwei	non-Xuanwei	Total	P
	(n = 139)	(n = 144)	(n = 283)	
Gender				
Male	87(62.59%)	121(84.03%)	208(73.50%)	< 0.000
Female	52(37.41%)	23(15.97%)	75(26.50%)	
Age				
< 65 years	110(79.14%)	97(67.36%)	207(73.14%)	0.025
≥ 65 years	29(20.86%)	47(32.64%)	76(26.86%)	
Smoking History				
Yes	59(42.45%)	67(46.53%)	126(44.52%)	0.490
No	80(57.55%)	77(53.47%)	157(55.48%)	
Comorbidities				
Yes	29(20.86%)	49(34.03%)	78(27.56%)	0.013
No	110(79.14%)	95(65.97%)	205(72.44%)	
ECOG PS Score				
0	1(0.72%)	5(3.47%)	6(2.12%)	< 0.000
1	119(85.61%)	74(51.39%)	193(68.20%)	
2	5(3.60%)	17(11.81%)	22(7.77%)	
3	1(0.72%)	1(0.69%)	2(0.71%)	
Unknown	13(9.35%)	47(32.64%)	60(21.20%)	
PD-L1 Expression				
Positive	1(0.72%)	8(5.56%)	9(3.18%)	0.022
0 ~ 50%	1(0.72%)	4(2.78%)	5(1.77%)	
≥ 50%	1(0.72%)	1(0.69%)	2(0.71%)	

ECOG PS: Eastern Cooperative Oncology Group performance status, PD-L1: programmed death-ligand 1, EGFR: epidermal growth factor receptor, KRAS: Kirsten rat sarcoma viral oncogene homolog, Her-2: Human Epidermal Growth Factor Receptor 2, BRAF: B-Raf proto-oncogene, TP53: tumor protein p53, ALK: anaplastic lymphoma kinase,MET: mesenchymal epithelial transition factor,RET: rearranged during transfection proto-oncogene, ROS1: ROS proto-oncogene 1, TNM Stage: Tumor-Node-Metastasis Stage, PD-1 inhibitor: Programmed cell death protein 1 inhibitor.

Clinical Characteristics	Xuanwei	non-Xuanwei	Total	P
	(n = 139)	(n = 144)	(n = 283)	
Negative	0	2(1.39%)	2(0.71%)	
Unknown	136(97.84%)	129(89.58%)	265(93.64%)	
Gene Mutation				
EGFR(+)	5(3.60%)	7(4.86%)	12(4.24%)	
KRAS(+)	22(15.83%)	9(6.25%)	31(10.95%)	
Her-2(+)	1(0.72%)	0	1(0.35%)	
BRAF(+)	1(0.72%)	2(1.39%)	3(1.06%)	
TP53(+)	4(2.88%)	3(2.08%)	7(2.47%)	
ALK(+)	2(1.44%)	2(1.39%)	4(1.41%)	
MET(+)	2(1.44%)	1(0.69%)	3(1.06%)	
RET(+)	0	2(1.39%)	2(0.71%)	
ROS1(+)	1(0.72%)	0	1(0.35%)	
Negative	7(5.04%)	22(15.28%)	29(10.25%)	
Unknown	101(72.66%)	101(70.14%)	202(71.38%)	
Pathology Type				
Adenocarcinoma	102(73.38%)	54(37.50%)	156(55.12%)	< 0.000
Squamous	34(24.46%)	82(56.94%)	116(40.99%)	
Unknown	3(2.16%)	8(5.56%)	11(3.89%)	
TNM Stage				
□	9(6.47%)	9(6.25%)	18(6.36%)	0.682
□	6(4.32%)	5(3.47%)	11(3.89%)	
□	36(25.90%)	49(34.03%)	85(30.04%)	
□	87(62.59%)	80(55.56%)	167(59.01%)	

ECOG PS: Eastern Cooperative Oncology Group performance status, PD-L1: programmed death-ligand 1, EGFR: epidermal growth factor receptor, KRAS: Kirsten rat sarcoma viral oncogene homolog, Her-2: Human Epidermal Growth Factor Receptor 2, BRAF: B-Raf proto-oncogene, TP53: tumor protein p53, ALK: anaplastic lymphoma kinase,MET: mesenchymal epithelial transition factor,RET: rearranged during transfection proto-oncogene, ROS1: ROS proto-oncogene 1, TNM Stage: Tumor-Node-Metastasis Stage, PD-1 inhibitor: Programmed cell death protein 1 inhibitor.

Clinical Characteristics	Xuanwei	non-Xuanwei	Total	P
	(n = 139)	(n = 144)	(n = 283)	
Unknown	1(0.72%)	1(0.69%)	2(0.71%)	
Line of Therapy				
First-line	81(58.27%)	110(76.39%)	191(67.49%)	0.003
Second-line	16(11.51%)	4(2.78%)	20(7.07%)	
Third-line or above	4(2.88%)	4(2.78%)	8(2.83%)	
Preoperative Neoadjuvant	7(5.04%)	8(5.56%)	15(5.30%)	
Postoperative Adjuvant	31(22.30%)	18(12.50%)	49(17.31%)	
PD-1 inhibitor Used				
Camrelizumab	38(27.34%)	41(28.47%)	79(27.92%)	0.431
Sintilimab	60(43.17%)	52(36.11%)	112(39.58%)	
Tislelizumab	41(29.50%)	51(35.42%)	92(32.51%)	
Combined with Radiotherapy				0.029
Yes	18(12.95%)	33(22.92%)	51(18.02%)	
No	121(87.06%)	111(77.08%)	232(81.98%)	
Research Center				< 0.000
The First Affiliated Hospital of Kunming Medical University	34(24.46%)	99(68.75%)	133(47.00%)	
The Third Affiliated Hospital of Kunming Medical University	105(75.54%)	45(31.25%)	150(53.00%)	

ECOG PS: Eastern Cooperative Oncology Group performance status, PD-L1: programmed death-ligand 1, EGFR: epidermal growth factor receptor, KRAS: Kirsten rat sarcoma viral oncogene homolog, Her-2: Human Epidermal Growth Factor Receptor 2, BRAF: B-Raf proto-oncogene, TP53: tumor protein p53, ALK: anaplastic lymphoma kinase,MET: mesenchymal epithelial transition factor,RET: rearranged during transfection proto-oncogene, ROS1: ROS proto-oncogene 1, TNM Stage: Tumor-Node-Metastasis Stage, PD-1 inhibitor: Programmed cell death protein 1 inhibitor.

Table 3
Patients' baseline characteristics after PSM

Clinical Characteristics	Xuanwei (n = 78)	non-Xuanwei (n = 78)	Total (n = 156)	P
Gender				0.848
Male	61	60	121	
Female	17	18	35	
Age				0.853
< 65 years	59	58	117	
≥ 65 years	19	20	39	
Smoking History				0.772
Yes	36	35	71	
No	42	43	85	
Comorbidities				0.596
Yes	24	21	45	
No	54	57	111	
ECOG PS Score				0.289
0	1	5	6	
1	60	53	113	
2	5	8	13	
3	1	0	1	
Unknown	11	12	23	
PD-L1 Expression				1.000
Positive	1	2	3	
0 ~ 50%	1	1	2	
≥ 50%	1	0	1	

ECOG PS: Eastern Cooperative Oncology Group performance status, PD-L1: programmed death-ligand 1, EGFR: epidermal growth factor receptor, KRAS: Kirsten rat sarcoma viral oncogene homolog, Her-2: Human Epidermal Growth Factor Receptor 2, BRAF: B-Raf proto-oncogene, TP53: tumor protein p53, ALK: anaplastic lymphoma kinase,MET: mesenchymal epithelial transition factor,RET: rearranged during transfection proto-oncogene, ROS1: ROS proto-oncogene 1, TNM Stage: Tumor-Node-Metastasis Stage.

Clinical Characteristics	Xuanwei	non-Xuanwei	Total	P
	(n = 78)	(n = 78)	(n = 156)	
Negative	0	1	1	
Unknown	75	74	149	
Pathology Type				0.305
Adenocarcinoma	43	37	80	
Squamous	32	40	72	
Unknown	3	1	4	
TNM Stage				0.292
	3	4	7	
	3	0	3	
	22	29	51	
	49	45	94	
Unknown	1	0	1	
Line of Therapy				0.218
First-line	58	53	111	
Second-line	9	4	13	
Third-line or above	1	2	3	
Preoperative Neoadjuvant	2	6	8	
Postoperative Adjuvant	8	13	21	
Combined with Radiotherapy				1.000
Yes	13	13	26	
No	65	65	130	

ECOG PS: Eastern Cooperative Oncology Group performance status, PD-L1: programmed death-ligand 1, EGFR: epidermal growth factor receptor, KRAS: Kirsten rat sarcoma viral oncogene homolog, Her-2: Human Epidermal Growth Factor Receptor 2, BRAF: B-Raf proto-oncogene, TP53: tumor protein p53, ALK: anaplastic lymphoma kinase,MET: mesenchymal epithelial transition factor,RET: rearranged during transfection proto-oncogene, ROS1: ROS proto-oncogene 1, TNM Stage: Tumor-Node-Metastasis Stage.

Table 4 Combined therapy with PD-1 inhibitor

Treatment Regimen	Before PSM			After PSM		
	Xuanwei (n = 139)	non-Xuanwei (n = 144)	P	Xuanwei(n = 78)	non-Xuanwei (n = 78)	P
Treatment Regimen			0.218			0.754
PD-1 inhibitor monotherapy	1	2		0	1	
PD-1 inhibitor + Chemotherapy	103	113		60	59	
PD-1 inhibitor + Targeted therapy	1	2		1	1	
PD-1 inhibitor + Antiangiogenic therapy	1	0		0	0	
PD-1 inhibitor + Chemotherapy + Targeted therapy	3	6		3	1	
PD-1 inhibitor + Chemotherapy + Antiangiogenic therapy	20	9		8	6	
PD-1 inhibitor + Targeted therapy + Antiangiogenic therapy	1	0		0	0	
PD-1 inhibitor + Chemotherapy + Targeted therapy + Antiangiogenic therapy	9	12		6	10	

PD-1 inhibitor: Programmed cell death protein 1 inhibitor.

2.2 Analysis of Clinical Efficacy

2.2.1 Objective Response Evaluation

Following PSM, efficacy was evaluated in the 127 patients who received palliative treatment. The results (Table 5) showed that no patient achieved a complete response in either group. The overall ORR was 31.50%, and the DCR was 85.04%. Regarding the comparison of treatment efficacy between the two groups, no significant difference in ORR was observed between the Xuanwei group and the non-Xuanwei group (30.88% vs. 32.20%, P = 0.873). In contrast, the DCR was significantly higher in the Xuanwei group compared to the non-Xuanwei group (95.59% vs. 72.88%, P < 0.001).

Following PSM, the therapeutic efficacy of the three PD-1 inhibitors was evaluated separately in the Xuanwei and non-Xuanwei groups. The results (Table 6) showed that within the Xuanwei group, the DCR for both camrelizumab and sintilimab were significantly higher than those in the non-Xuanwei group (P = 0.006 and P = 0.027, respectively). No other statistically significant differences were observed.

Table 5
Objective efficacy evaluation

Clinical Efficacy	**After Propensity Score Matching**		
	Xuanwei (n = 68)	**non-Xuanwei (n = 59)**	**P**
CR	0	0	
PR	21	19	
SD	44	24	
PD	3	16	
ORR	30.88%	32.20%	0.873
DCR	95.59%	72.88%	0.000

CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease, ORR: efficacy endpoints included the objective response rate, DCR: disease control rate.

Table 6
Objective efficacy evaluation of Camrelizumab subgroup, Sintilimab subgroup and Tislelizumab subgroup after PSM

PD-1 inhibitor	Xuanwei			non-Xuanwei			P
	CR + PR	SD	PD	CR + PR	SD	PD	
Camrelizumab	3	12	0	3	4	5	
ORR	20.00%			25.00%			0.756
DCR	100.00%			58.33%			0.006
Sintilimab	9	17	1	6	12	6	
ORR	33.33%			25.00%			0.514
DCR	96.30%			75.00%			0.027
Tislelizumab	9	15	2	10	8	5	
ORR	34.62%			43.48%			0.525
DCR	92.31%			78.26%			0.161

CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease, ORR: efficacy endpoints included the objective response rate, DCR: disease control rate, PD-1 inhibitor: Programmed cell death protein 1 inhibitor.

2.2.2 Analysis of PFS outcomes in palliative care patients

Among the 127 patients receiving palliative treatment included after PSM, the median PFS was 27 months, with a mean PFS of 31.83 months. In the Xuanwei group, the median PFS was not reached, and the mean PFS was 28.52 months. In contrast, the non-Xuanwei group had a median PFS of 20 months and a mean PFS of 29.28 months (Fig. 2A). The Log-rank test showed no significant difference in PFS between the two groups (P = 0.249).

The PFS curves for the 127 patients receiving palliative treatment (Fig. 2B) revealed the following: the camrelizumab group had a median PFS of 24 months and a mean PFS of 24.73 months; the sintilimab group had a median PFS of 20 months and a mean PFS of 36.62 months; and the median PFS was not reached in the tislelizumab group, with a mean PFS of 26.58 months. The Log-rank test indicated no significant difference in PFS among the three PD-1 inhibitors (P = 0.342).

2.2.3 Analysis of Factors Influencing PFS

To identify factors influencing PFS in the 127 patients receiving palliative treatment, Kaplan-Meier survival curves were plotted according to different clinical characteristics, and the median PFS was estimated. Univariate analysis was performed using the Log-rank test. The results (Table 7) showed that PD-L1 expression status (P = 0.008) and the administration of concurrent radiotherapy (P < 0.001) were

significantly associated with patient PFS. No significant associations were found between PFS and any of the other evaluated indicators ($P > 0.05$).

To further analyze the independent impact of various factors on PFS, a multivariate Cox regression analysis was performed, incorporating factors identified from the univariate analysis and those considered clinically relevant. The results (Table 8) demonstrated that the administration of concurrent radiotherapy was an independent prognostic factor for PFS ($P = 0.001$). None of the other factors examined were identified as independent influencing factors for PFS.

Table 7
Different clinical features were analyzed by stratification with PFS as endpoints

Clinical feature	Frequency	Median PFS (months)	P
All patients	127	27	
Gender			0.713
Male	99	24	
Female	28	32	
Age			0.223
< 65 years	98	27	
≥ 65 years	29	Median PFS not reached	
Smoking history			0.781
Yes	60	23	
No	67	27	
Comorbidities			0.525
Yes	40	18	
No	87	32	
ECOG PS Score			0.916
0 or 1	104	27	
2 or 3	13	18	
Unknown	10	23	
PD-L1 expression			0.008
Positive	5	15	
Negative	1	4	
Not specified	121	27	
TNM stage			0.306
I or II	2	Median PFS not reached	
	37	Median PFS not reached	
	87	24	

ECOG PS: Eastern Cooperative Oncology Group performance status, PD-L1: programmed death-ligand 1, TNM Stage: Tumor-Node-Metastasis Stage.

Clinical feature	Frequency	Median PFS (months)	P
Unknown	1	14	
Pathology type			0.602
Adenocarcinoma	69	27	
Squamous	56	Median PFS not reached	
Unknown	2	23	
Line of therapy			0.281
First-line	111	24	
Second-line	13	47	
Third-line or above	3	10	
Combined with radiotherapy			< 0.000
Combined radiotherapy	25	12	
No combined radiotherapy	102	32	

ECOG PS: Eastern Cooperative Oncology Group performance status, PD-L1: programmed death-ligand 1, TNM Stage: Tumor-Node-Metastasis Stage.

Table 8
Multivariate Cox regression analysis with PFS as the endpoint

Influencing factor	95% CI	P value
Gender	0.368–1.787	0.603
Age	0.343–1.591	0.439
Smoking history	0.326–1.436	0.316
Comorbidities	0.497–1.725	0.808
ECOG score	0.593–1.463	0.758
PD-L1 expression	0.556–2.011	0.866
TNM stage	0.901–3.250	0.101
Pathology type	0.430–1.603	0.580
Line of therapy	0.384–1.775	0.624
Combined radiotherapy	0.188–0.661	0.001

ECOG PS: Eastern Cooperative Oncology Group performance status, PD-L1: programmed death-ligand 1, TNM Stage: Tumor-Node-Metastasis Stage. 95% CI 95% confidence interval.

2.2.4 OS outcomes in palliative care patients

OS was analyzed in the 156 patients included after propensity score matching. The median OS for the entire cohort was 47 months, with a mean OS of 46.53 months. The results (Fig. 3) showed that in the Xuanwei group, the median OS was not reached, and the mean OS was 38.44 months. In contrast, the non-Xuanwei group had a median OS of 47 months and a mean OS of 45.82 months. The Log-rank test revealed no significant difference in OS between the two groups (P = 0.980).

2.3 Analysis of Treatment-Related Adverse Events

2.3.1 Overall Adverse Event Profile

Adverse events (AEs) were assessed in all 156 enrolled patients. As summarized in Table 9, the overall incidence of AEs was 21.79% (34/156). Most AEs were Grade 1 or 2 in severity, with an incidence of 20.51% (32/156). The incidence of Grade ≥ 3 AEs was 1.28% (2/156). No Grade 5 (fatal) AEs were reported. A total of 18 AEs occurred in the Xuanwei group, compared with 16 AEs in the non-Xuanwei group. A direct comparison of the overall AE incidence rates between the two groups (Table 10) showed no statistically significant difference (21.79% vs. 20.51%, P = 0.832).

Furthermore, the incidence of AEs for each individual PD-1 inhibitor (camrelizumab, sintilimab, and tislelizumab) was compared between the Xuanwei and non-Xuanwei groups (Table 11). No significant differences were found for any of the three agents (P > 0.05).

Table 9
Immune-Related Adverse Events

Adverse Event	Xuanwei (n = 78)		non-Xuanwei (n = 78)		All Patients (n = 156)
	Grade 1–2	Grade ≥ 3	Grade 1–2	Grade ≥ 3	Overall Incidence
Dermatologic toxicity	6	1	6	1	8.97%
Thyroid toxicity	7	0	5	0	7.69%
Hepatic toxicity	1	0	2	0	1.92%
Renal toxicity	0	0	0	0	0
Gastrointestinal toxicity	0	0	0	0	0
Respiratory	2	0	1	0	1.92%
Infusion reaction	0	0	0	0	0
Cardiac toxicity	1	0	0	0	0.64%
Other	0	0	1	0	0.64%
None.					

Note

Other occurring immune-related adverse reactions included thrombocytopenia, visual impairment, adrenal insufficiency, sex hormone disorders, immune-mediated hypophysitis, and hyperglycemia.

Table 10
Comparison of all adverse reactions between the two groups

Group	Adverse Reactions				Total		P
	Occurred		Not Occurred				
Xuanwei	14	17.95%	64	82.05%	78	50%	0.832
non-Xuanwei	13	16.67%	65	83.33%	78	50%	
None.							

Table 11
Comparison of adverse reactions ofCamrelizumab subgroup, Sintilimab subgroup and Tislelizumab subgroup

PD-1 inhibitor	Xuanwei		non-Xuanwei		Total	P
	Occurred	Not Occurred	Occurred	Not Occurred		
Camrelizumab	4	16	2	16	38	0.663
Sintilimab	7	23	6	21	57	0.920
Tislelizumab	3	25	5	28	61	0.715
PD-1 inhibitor: Programmed cell death protein 1 inhibitor.						

2.3.2 Univariate Analysis of ADRs

A univariate analysis was performed using the Log-rank test to assess the correlation between the occurrence of ADRs and PFS. The results (Table 12) indicated that there was no statistically significant difference in median PFS between patients who experienced ADRs and those who did not (P = 0.073).

Table 12
adverse events were analyzed by stratification with PFS as endpoints

Clinical feature	Frequency	Median PFS (months)	P
All patients	127	27	
Occurrence of adverse events			
Occurred	25	15	0.073
Not occurred	102	32	
PFS: progression-free survival			

3 Discussion

This study is the first to compare the efficacy and safety of camrelizumab, sintilimab, and tislelizumab in patients with NSCLC from Xuanwei and non-Xuanwei regions using real-world data. The results showed that in terms of efficacy, the DCR was significantly higher in the Xuanwei group than in the non-Xuanwei group ($P < 0.05$), primarily manifested as better efficacy of camrelizumab and sintilimab in the Xuanwei group ($P < 0.05$). No significant differences were observed in the ORR, OS, and PFS between the two groups. Regarding safety, the incidence of adverse events was similar between the two groups and predominantly mild to moderate in severity.

In terms of efficacy evaluation, the overall ORR for all patients was 31.50%, and the DCR was 85.04%. The ORR was lower than reported in previous clinical trials, while the DCR was similar (10, 11). A retrospective study (12) reported an overall ORR of 58.1% and a DCR of 83.9% for PD-1 inhibitors

combined with other drugs in a real-world setting, with the ORR being higher than in this study, but the DCR being close to our results. The reason for this discrepancy may be that this study primarily included NSCLC patients receiving first-line treatment, although a small number of patients receiving second- and third-line therapies were also included. Despite the relatively low number of patients achieving CR and PR in this study, the majority achieved SD, indicating good disease control.

The DCR was significantly higher in patients from the Xuanwei region compared to those from non-Xuanwei regions. We speculate that this may be related to the unique genetic mutation profile, high PD-L1 expression, and immune microenvironment in the Xuanwei region. The gene mutation rate and patterns in this region differ significantly from those in non-Xuanwei areas (13, 14), potentially endowing NSCLC patients from Xuanwei with distinctive features in their response to immunotherapy. Residents in the Xuanwei region are chronically exposed to high concentrations of polycyclic aromatic hydrocarbon carcinogens generated from indoor coal combustion. This not only increases their tumor mutational burden (TMB) (15) but also places these patients in a state of chronic inflammation induced by environmental exposure. Key cytokines released by activated immune cells, such as interferon-gamma, can upregulate PD-L1 expression through activation of the classic JAK-STAT signaling pathway (16, 17). Previous studies have also shown that the positive PD-L1 expression rate (PD-L1 > 1%) in NSCLC patients from the Xuanwei region is significantly higher than that in East Asian patients (5, 8, 9). Therefore, when Xuanwei patients are treated with PD-1 monoclonal antibodies, the drugs can effectively block the key immunosuppressive PD-1/PD-L1 signaling pathway, potentially leading to more pronounced efficacy.

Evaluating the efficacy of the three PD-1 inhibitors separately in the two groups revealed that the DCR for camrelizumab and sintilimab was significantly higher in the Xuanwei group than in the non-Xuanwei group, while no significant difference in DCR was observed for tislelizumab between the two groups. Notably, the DCR for camrelizumab and sintilimab in Xuanwei patients was also slightly higher than reported in previous clinical trials and real-world studies (10, 12, 18, 19). We speculate that this may be related to the antibody structure and the unique tumor immune microenvironment in the Xuanwei region. Studies suggest that Fc segment engineering is a key factor influencing the efficacy of immune checkpoint inhibitors (20–22). Among the three PD-1 inhibitors used in this study, camrelizumab and sintilimab retain the ability of their Fc segments to bind to Fc gamma receptors (FcγR), while tislelizumab is designed with a silenced Fc segment. Research has confirmed that compared to durvalumab, which uses a silenced Fc segment, avelumab, which retains Fc segment binding to FcγR, can more effectively activate natural killer (NK) cells and induce higher levels of tumor cell cytotoxicity, which may contribute to its superior antitumor effects (20, 23). Therefore, we hypothesize that in the unique inflammatory microenvironment characterized by high PD-L1 expression in Xuanwei NSCLC patients, camrelizumab and sintilimab, with their functional Fc segments, can leverage their Fc segment's ability to bind FcγR to activate immune effector cells such as NK cells, thereby yielding better therapeutic outcomes for patients. In contrast, tislelizumab, with its silenced Fc segment, cannot exploit this microenvironmental advantage, resulting in no significant difference in efficacy between the Xuanwei and non-Xuanwei regions. This hypothesis provides a new direction for future research on PD-1

inhibitors in treating NSCLC in the Xuanwei region. Whether this speculation holds true has not been reported in related studies and requires further validation through basic experiments and clinical research.

Long-term efficacy evaluation showed no statistically significant differences in PFS or OS between the two groups. The PFS in this study was significantly longer than that reported in prospective clinical studies (24–26). This discrepancy may be attributed to the relatively short follow-up period, with most patients not yet reaching the endpoint events, and the presence of some censored data. Previous studies investigating the efficacy and adverse events of camrelizumab (27, 28), sintilimab (29), and tislelizumab (18, 30), combined with chemotherapy versus chemotherapy alone as first-line treatment for advanced NSCLC have shown that PD-1 inhibitor combination therapy significantly prolongs PFS, which is largely consistent with our findings. The median OS for the 156 matched patients was 47 months, with no statistically significant difference between groups. The OS in this study was significantly longer than in previous clinical studies (24), possibly because this study included patients receiving neoadjuvant therapy before surgery and adjuvant therapy after surgery. These patients had earlier stages and milder disease, leading to significantly longer OS compared to those receiving palliative care. Comparing the PFS of patients using the three different inhibitors revealed no statistically significant differences.

Analysis of factors influencing PFS showed that in univariate analysis, PD-L1 expression status ($P = 0.008$) and whether combined with radiotherapy ($P < 0.000$) were significantly associated with PFS, while no significant differences in PFS were found among other indicator groups. Subsequently, multivariate Cox regression analysis was performed based on the univariate analysis results and clinical practice. The results indicated that patients not receiving combined radiotherapy ($P = 0.001$) experienced disease progression later and had longer PFS. None of the other factors were independent influencing factors for PFS. In this study, due to limited sample size, PD-L1 expression levels were not further stratified and were only categorized as positive or negative. Although 92.24% of patients had unknown PD-L1 expression status due to incomplete medical records, loss of data, or lack of genetic testing, the univariate analysis still suggested an association between PD-L1 expression and PFS. Future studies need to expand the sample size to explore whether differences in efficacy and prognosis exist among patients with different PD-L1 expression levels.

Regarding safety, the overall incidence of adverse events was 21.79%. Comparison of adverse event incidence between the two groups showed no statistically significant difference. The incidence was similar between groups, with the vast majority being grade 1–2 (incidence 20.51%), and grade 3 or higher adverse events occurring in only 1.28% of patients. PD-1 inhibitor combination therapy was generally manageable with a controllable safety profile, and no fatal adverse events occurred. The overall incidence of adverse events observed in this study was similar to that in clinical trials, but the incidence of severe adverse events was lower than reported in clinical trials (24–26). Log-rank univariate analysis of the correlation between adverse events and PFS showed no significant correlation between patients who experienced adverse events and those who did not.

This study is a retrospective investigation of PD-1 inhibitor use in NSCLC patients from Xuanwei and non-Xuanwei regions in a real-world setting and has several limitations: As a retrospective analysis, biases such as selection bias and information collection bias are inevitable and may impact the results. Additionally, the high proportion of patients with unknown PD-L1 and other gene expression statuses, the lack of detailed subgroup analysis in the study design, the relatively short follow-up for some patients leading to immature PFS and OS data, and the presence of censored data in the survival analysis may all affect the outcomes. It is important to note that the comparison of this study's results with those of clinical trials is not a strict head-to-head comparison. Compared to randomized controlled trials, this study involves more confounding factors. Future research needs to accumulate more real-world data for a more in-depth investigation of efficacy and adverse events.

To address these limitations, subsequent studies could further expand the sample size, extend the follow-up period, obtain more complete data, and conduct detailed subgroup analyses to provide stronger reference evidence for clinical medication decisions.

4 Conclusions

This study revealed that NSCLC patients from the Xuanwei region achieved a higher disease control rate (DCR) with PD-1 inhibitor therapy. Furthermore, significant differences in clinical efficacy were observed among different types of PD-1 monoclonal antibodies, particularly for camrelizumab and sintilimab. These findings suggest that the therapeutic response to PD-1 inhibitors in NSCLC patients from the Xuanwei region may possess distinctive characteristics.

Abbreviations

full English designation	English abbreviation
non-small cell lung cancer	NSCLC
Programmed Cell Death-1 Inhibitor	PD-1 inhibitor
Chinese Pharmacovigilance System	CHPS
objective response rate	ORR
disease control rate	DCR
progression-free survival	PFS
Median overall survival	OS
programmed death-ligand 1	PD-L1
propensity score matching	PSM
complete response	CR
partial response	PR
stable disease	SD
progressive disease	PD
Adverse drug reactions	ADRs
Adverse events	AEs

Declarations

Ethics approval and consent to participate

The retrospective study was performed in a tertiary Chinese hospital (The First Affiliated Hospital of Kunming Medical University). The Ethics Committee of The First Affiliated Hospital of Kunming Medical University reviewed the study and granted approval (Approval Number: 2026L126). The need for consent to participate was also waived by the Ethics Committee of The First Affiliated Hospital of Kunming Medical University which approved the study, because it found the non-interventional retrospective study to entail minimal risk. The ethical standards of the Declaration of Helsinki were adhered to ensure the maintenance of patient data privacy and confidentiality throughout the course of this study.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing Interests

The authors declare that they have no competing interests.

Funding

This study was supported by the National Natural Science Foundation of China, Project Title: Metformin regulates placental glucose transport by improving placental mitochondrial function in gestational diabetes mellitus patients **(No. 8216060310), Yunnan health training project of high level talents (No. D-2024010).**

Authors' contributions

All authors contributed to the study conception and design. Material preparation and data collection were performed by XYL, SJK, XP and FL. Data analysis was performed by JH, JL and SSL. The first draft of the manuscript was written by XW, JH and FL, and revised by XW and SJK. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Acknowledgements:

Not applicable.

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Figures

The patient screening flowchart is presented in Figure 1.

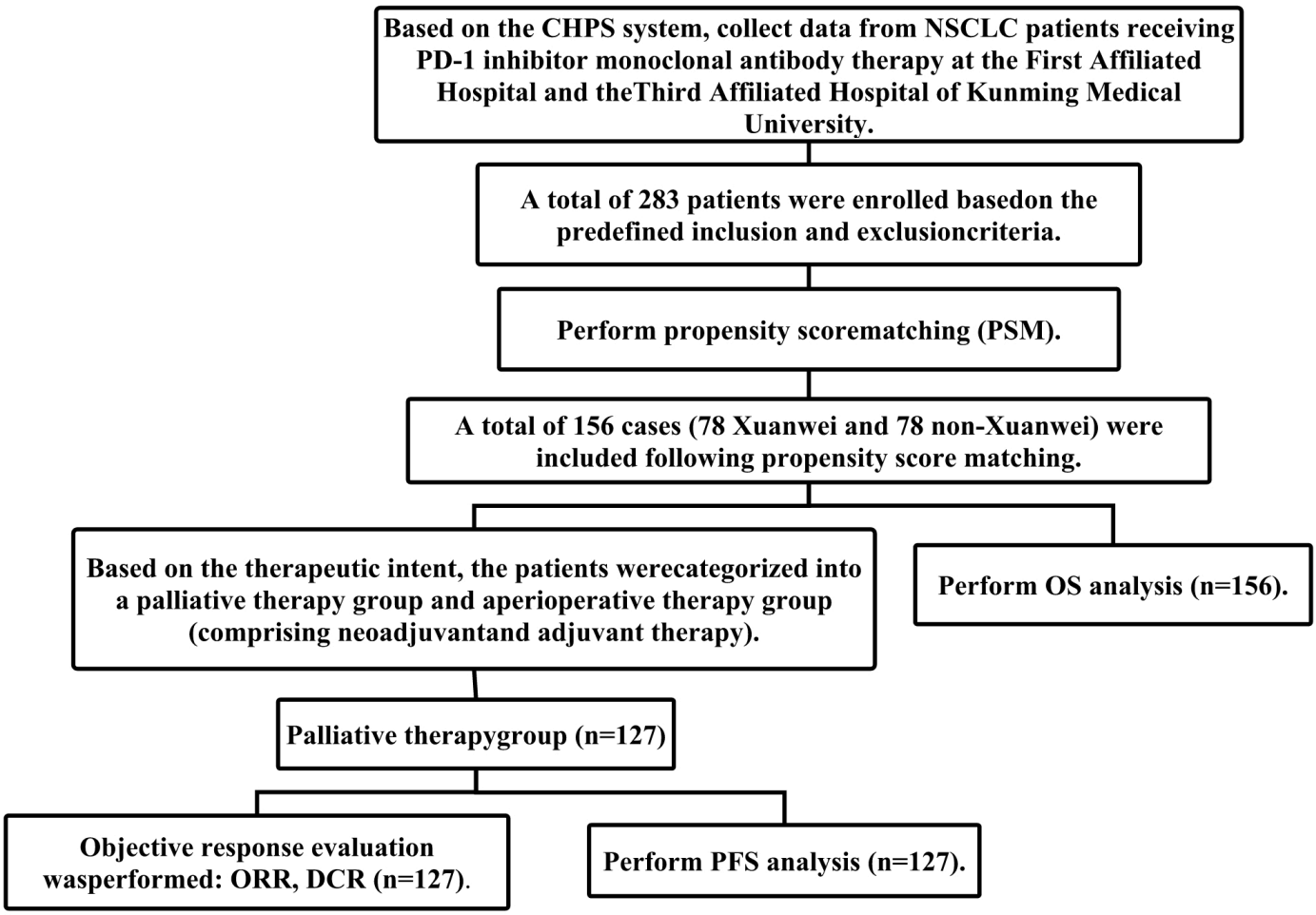


Figure 1

The patient screening flowchart.

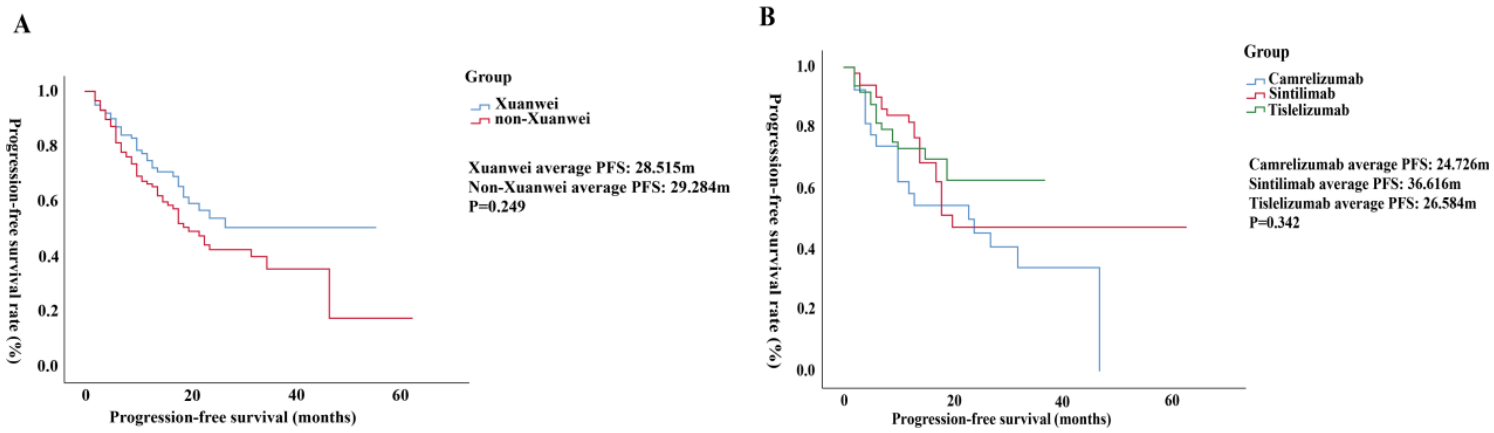


Figure 2

Kaplan-Meier curves of PFS in patients with NSCLC. A: PFS curves of the Xuanwei group and the non-Xuanwei group. B: PFS Curves of Camrelizumab, Sintilimab, and Tislelizumab. PFS: progression-free survival.

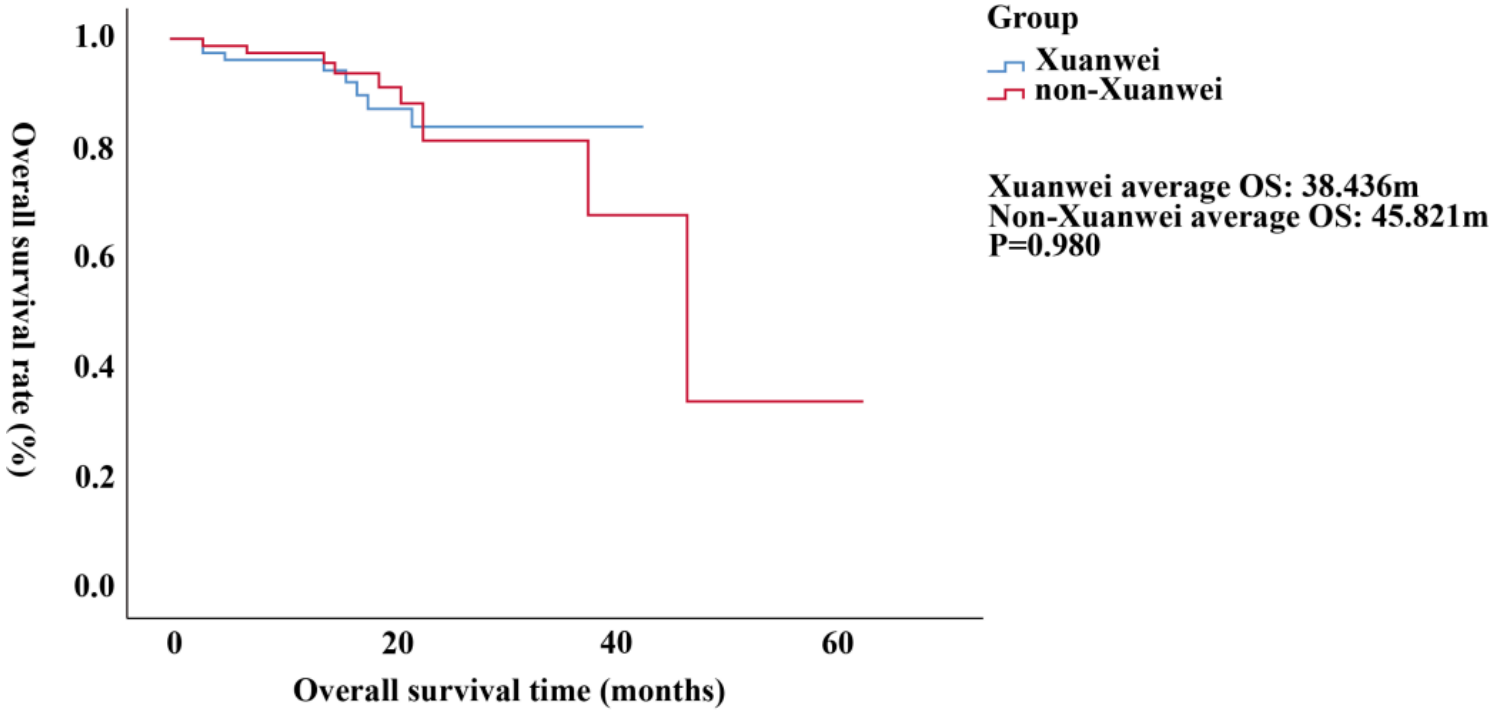


Figure 3

Kaplan-Meier curves of OS in patients with NSCLC in the Xuanwei group and the non-Xuanwei group. OS: overrall survival.