Research Article

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Bevacizumab/PD-1 inhibitor plus chemotherapy as first-line treatment of advanced non-squamous non-small-cell lung cancer

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Aim: To compare the effectiveness of PD-1 inhibitor or bevacizumab plus chemotherapy in advanced non-squamous non-small cell lung cancer (nsNSCLC). **Methods:** We retrospectively collected data for patients with advanced nsNSCLC who underwent first-line treatment with PD-1 inhibitor or bevacizumab plus chemotherapy (IC and BC groups). Propensity score matching (PSM) was adopted to balance covariates. **Results:** 278 patients were enrolled, after PSM (n = 104/group), the objective response rate was 45.1% and 24.0% in the IC and BC groups (p = 0.001). Median progression-free survival (PFS) was 13.5 and 8.2 months (p = 0.007), and duration of response was 14.8 versus 8.1 months (p = 0.007), respectively. In subgroup analysis, the PFS for those patients with PD-L1≥1% (16.2 vs 6.8 months, p = 0.000) was significantly longer in the IC group than that in BC group, but not in the PD-L1<1% subgroup (8.9 vs12.7 months, p = 0.719). **Conclusion:** PD-1 inhibitor plus chemotherapy was superior to bevacizumab plus chemotherapy as first-line treatment for advanced nsNSCLC, which is debatable for patients with PD-L1<1%.

Plain language summary

What is this article about? Whether PD-1 immune checkpoint inhibitor plus chemotherapy is superior to bevacizumab plus chemotherapy as first-line treatment for advanced non-squamous non-small cell lung cancer (nsNSCLC) remains unclear. The study aimed to compare the effectiveness of the two regimens in advanced nsNSCLC.

What were the results? We found that PD-1-targeted immune checkpoint inhibitor plus chemotherapy was superior to bevacizumab plus chemotherapy as first-line treatment for advanced nsNSCLC without driver gene mutations, however this conclusion is debatable for patients with PD-L1<1%.

What do the results of the study mean? Current clinical studies that directly comparing PD-1 inhibitor plus chemotherapy and bevacizumab plus chemotherapy are lacking. It is still unclear which of these two regimens was superior as first-line treatment for advanced nsNSCLC, especially for patients with PD-L1<1%. This study confirmed that PD-1 inhibitor plus chemotherapy was superior to bevacizumab plus chemotherapy for advanced non-squamous non-small cell lung cancer (nsNSCLC), but not for those patients with PD-L1<1%. Prospective studies are needed to determine which regimen is better for patients with PD-L1 <1%.

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Keywords: bevacizumab • immune checkpoint inhibitor • non-squamous non-small-cell lung cancer • PD-1

Lung cancer is the leading cause of cancer incidence and cancer-related death in China [1]. Non-small-cell lung cancer (NSCLC) accounts for approximately 80% of all lung cancers, and more than half of patients with NSCLC are diagnosed at an advanced stage [2]. Targeted therapy has greatly improved survival in patients with advanced NSCLC harboring driver gene mutations. Before the application of immune checkpoint inhibitors, the standard first-line treatment is platinum-based chemotherapy for patients without driver gene mutations; these treatments yield response rates of 17–36% and a median survival of 8–10 months [3,4]. Bevacizumab combined with chemotherapy prolongs the overall survival of non-squamous NSCLC (nsNSCLC) patients by 2 months compared with standard chemotherapy [5,6], and it was approved by the US FDA in 2006 for nsNSCLC. In the BEYOND study of Chinese patients, bevacizumab combined with paclitaxel and carboplatin significantly prolonged OS by 6.6 months compared with chemotherapy (24.3 vs 17.7 months, HR: 0.68, p = 0.0154) [7].

Immune checkpoint inhibitors (ICIs) that target PD-1 and PD-L1 have become new first-and second-line treatment options for NSCLC patients without driver gene mutations. In the KEYNOTE189 study, pembrolizumab plus pemetrexed and carboplatin/cisplatin significantly improved objective response rate (ORR) (48.3% vs 19.9%), median progression-free survival (PFS; 9 months vs 4.9 months, HR: 0.49; 95% CI: 0.41–0.59), and median OS (22 months vs 10.6 months, HR: 0.6, 95% CI: 0.46–0.69) compared with chemotherapy alone [8]. Additionally, clinical studies of ICIs targeting PD-1 combined with chemotherapy for first-line treatment of Chinese patients with advanced NSCLC have also achieved positive results, and camrelizumab, sintilimab, and tislelizumab have been approved by the China Food and Drug Administration (CFDA) for driver gene–negative advanced nsNSCLC [9–11]. However, most of these studies compared ICI plus chemotherapy with chemotherapy, and there have been a lack of studies that performed a direct comparison with bevacizumab plus chemotherapy. Only one study, the Impower150 study, examined atezolizumab (a PD-L1 antibody) or bevacizumab combined with paclitaxel plus carboplatin regimens and reported a similar OS and PFS between the two regimens [12]. Whether anti-PD-1 ICI combined with chemotherapy is superior to bevacizumab combined with chemotherapy remains unclear. Therefore, we conducted this real-world retrospective study to compare the two regimens in patients with advanced nsNSCLC.

Materials & methods

Study design & patients

We retrospectively collected patients with advanced NSCLC who were diagnosed and treated at Tianjin Medical University Cancer Institute & Hospital from March 2017 to November 2021. The inclusion criteria were as follows: ≥18 years of age; pathologically or cytologically confirmed stage IIIB/IIIC/IV nsNSCLC; first-line treatment was ICI combined with chemotherapy or bevacizumab combined with chemotherapy, and completion of at least one cycle of combination treatment; ≥ one measurable target lesion following the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1); and without sensitizing EGFR mutations or ALK or ROS1 gene rearrangement. The exclusion criteria were as follows: NSCLC concurrent with other malignancy; incomplete clinical data; previously received targeted therapy as first-line treatment; uncontrolled brain or meningeal metastases; no data (for example, images) or records to confirm treatment response.

Treatment & assessment

The patients were divided into two groups depending on the treatment regimens: ICIs targeting PD-1 plus chemotherapy (the IC group) and bevacizumab plus chemotherapy (the BC group). PD-1-targeting immune checkpoint inhibitors included pembrolizumab, camrelizumab, sintilimab, or tislelizumab. Platinum-based chemotherapy included pemetrexed plus platinum (carboplatin/cisplatin/nedaplatin), paclitaxel plus platinum, and nab-paclitaxel plus platinum. Patients treated with non-platinum-based single-agent chemotherapy plus ICI or bevacizumab were allowed to be included in the study. All patients were treated at a standard dose following clinical guidelines in China.

Tumor response was assessed every two cycles by imaging, mainly including CT of chest and upper abdomen, brain MRI or CT with contrast. Response was determined as complete response (CR), partial response (PR), progressive disease (PD), or stable disease (SD) following RECIST 1.1. The ORR was calculated as the percentage of CR and PR. The disease control rate (DCR) was determined as the percentage of CR, PR, and SD. Progression free survival (PFS) was defined as the time from the start of treatment to PD or death from any cause. Overall survival (OS) was defined as the time from start of treatment to death. Duration of response (DOR) was measured from the time measurement criteria were first met for CR/PR until PD or death from any cause. The primary end

points were PFS and ORR, and the secondary end points were OS and DOR. Considering that adverse reactions may be poorly documented in medical records and recall of previous events may be unreliable, only adverse reactions leading to discontinuation or dose reduction were recorded in this study. Adverse reactions were graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Data collection

Data were collected from patients' electronic medical records. Patient details included sex, age, smoking history, ECOG PS, histological subtype, stage, metastatic site, gene mutation status, and PD-L1 expression. The start time of treatment, time to disease progression, time to death, number of cycles, reasons for discontinuation, best response, and time to PR or CR were also recorded. The date of disease progression was recorded as the date that the clinician cited as the first source of proof for progression, such as imaging report, or the clinician recorded date when there was no source of evidence.

Statistical analysis

Statistical analyses were performed using SPSS 26.0, and GraphPad Prism 9 was used for plotting. Propensity score matching (PSM) was done using R4.2.2. Survival curves were plotted by the Kaplan–Meier method and compared using the log-rank test. Hazard ratio (HR) and 95% confidence interval (CI) were estimated using Cox proportional regression model. Univariate and Multivariate analysis of survival outcomes was performed using Cox proportional hazards model. Qualitative or categorical variables were compared using the Chi-square test. Two-sided test $p < 0.05$ was considered statistically different.

Results

Patient characteristics

A total of 278 patients were included in this study. Of the total patient group, 127 patients were in the IC group and 151 patients were in the BC group. The baseline factors were not balanced between the two groups, so we adopted PSM. Factors included in PSM were sex, age, smoking history, ECOG, stage, brain metastases, liver metastases, bone metastases, EGFR mutation status, PD-L1, and chemotherapy regimen. The baseline characteristics before and after PSM in both groups are shown in Table 1.

In the IC group, eight (6.3%) patients were treated with ICI plus pemetrexed or paclitaxel mono-chemotherapy, and the other (93.7%) patients received ICI plus platinum-based regimens. 121 (95.3%) patients received combination therapy containing pemetrexed, 2 (1.6%) patients were treated with paclitaxel/carboplatin and ICI, and 4 (3.1%) patients received nab-paclitaxel/carboplatin and ICI. In the BC group, 7 (4.6%) patients received bevacizumab plus pemetrexed or paclitaxel mono-chemotherapy, and the others (95.4%) were treated with bevacizumab plus platinum-based chemotherapy. 126 (83.4%) patients received combination regimens of pemetrexed, 24 (15.9%) patients were treated with paclitaxel-combination therapy, and 1 (0.7%) patient received nab-paclitaxel/carboplatin.

Effectiveness of treatment

The following analyses were all performed in the PSM population.

Patients were followed up until 30 September 2022. Approximately 85.6% (89/104) in the IC group and 90.3% (94/104) in the BC group completed at least four cycles of the combination treatment. The ORR was 45.1% (47/104) in the IC group and 24.0% (25/104) in the BC group ($p = 0.001$). The DCR was 90.2% (94/104) and 95.1% (99/104) in the IC and BC groups, respectively ($p = 0.180$) (Table 2).

The median follow-up time was 15.4 months (95% CI: 13.8–17.0 months) in the IC group and 19.3 months (95% CI: 11.8–26.3 months) in the BC group. The median PFS was 13.5 months (95% CI: 10.9–16.1 months) in the IC group and 8.2 months (95% CI: 6.3–10.1 months) in the BC group, with a statistically significant difference between groups ($p = 0.007$) (Figure 1). There was no difference in OS between the two groups (not reached in the IC group and 28.7 months in the BC group, $p = 0.083$) (Figure 2). We also observed a significant difference in DOR, with 14.8 months (95% CI: 10.7–18.9 months) in the IC group and 8.1 months (95% CI: 6.7–9.5 months) in the BC group ($p = 0.007$).

Univariate and multivariate cox regression analysis associated with PFS was performed and included the following factors: age, sex, EGOG score, smoking history, stage, brain metastasis, liver metastasis, bone metastasis and treatment regimens. Given the immaturity of OS data (25%) in the IC group, we did not perform a cox regression

Table 1. Demographic and disease characteristics of the patients at baseline.

	Before PSM			After PSM		
	IC group n = 127 (%)	BC group n = 151 (%)	p-value	IC group n = 104 (%)	BC group n = 104 (%)	p-value
Sex			0.999			0.878
Male	90 (70.9)	107 (70.9)		73 (70.2)	75 (72.1)	
Female	37 (29.1)	44 (29.1)		31 (29.8)	29 (27.9)	
Age			0.656			0.662
<65 years	80 (63.0)	99 (65.6)		66 (63.5)	70 (67.3)	
≥65 years	47 (37.0)	52 (34.4)		38 (36.5)	34 (32.7)	
ECOG			0.011			0.880
0	94 (74.0)	90 (59.6)		74 (71.2)	72 (69.2)	
1	33 (26.0)	61 (40.4)		30 (28.8)	32 (30.8)	
Smoking status			0.146			0.886
Former or current	84 (66.1)	87 (57.6)		67 (64.4)	65 (62.5)	
Never	43 (33.9)	64 (42.4)		37 (35.6)	39 (37.5)	
Stage			0.193			0.795
IIIB/IIIC	14 (11.0)	10 (6.6)		7 (6.7)	9 (8.7)	
IV	113 (89.0)	141 (93.4)		97 (93.3)	95 (91.3)	
Pathology			0.527			0.307
Adenocarcinoma	123 (96.9)	144 (95.8)		101 (97.1)	98 (94.2)	
Others	4 (3.1)	7 (4.2)		3 (2.9)	6 (5.8)	
Brain metastases			0.922			0.828
No	114 (89.8)	135 (89.4)		93 (89.4)	91 (87.5)	
Yes	13 (10.2)	16 (10.6)		11 (10.6)	13 (12.5)	
Liver metastases			0.199			1.000
No	111 (87.4)	139 (92.1)		92 (88.5)	93 (89.4)	
Yes	16 (12.6)	12 (7.9)		12 (11.5)	11 (10.6)	
Bone metastases			0.198			0.667
No	79 (62.2)	105 (69.5)		67 (64.4)	63 (60.6)	
Yes	48 (37.8)	46 (30.5)		37 (35.6)	41 (39.4)	
EGFR-sensitive mutation			0.001			0.704
No	94 (74.0)	135 (89.4)		86 (82.7)	89 (85.6)	
Unknown	33 (26.0)	16 (10.6)		18 (17.3)	15 (14.4)	
PD-L1 TPS%			0.001			0.012
PD-L1<1%	11 (8.7)	24 (15.9)		10 (9.6)	14 (13.5)	
PD-L1 1–49%	14 (11.0)	15 (10.0)		13 (12.5)	13 (12.5)	
PD-L1≥50%	24 (18.9)	7 (4.6)		22 (21.2)	6 (5.8)	
Unknown	78 (61.4)	105 (69.5)		59 (56.7)	71 (68.2)	
Chemotherapy regimens			0.541			0.746
Platinum-based	119 (93.7)	144 (95.4)		100 (96.2)	98 (94.2)	
Single agent	8 (6.3)	7 (4.6)		4 (3.8)	6 (5.8)	

BC: Bevacizumab plus chemotherapy; IC: PD-1 inhibitor plus chemotherapy; TPS: Tumor cell proportion score; ECOG: Eastern Cooperative Oncology Group; PSM: Propensity score matching.

analysis for OS. The analysis showed that brain metastasis, liver metastasis, bone metastasis, and treatment regimens were independent prognostic factors for PFS in both univariate and multivariate cox regression analysis (Table 3).

Subgroup analysis of patients with brain metastasis, liver metastasis, and bone metastasis showed that the median PFS was similar between the IC and BC groups, whereas PFS tended to be longer in the IC group without metastases than that in the BC group (Figure 3). All subgroup analyses were showed in Figure 3.

Table 2. Summary of treatment effectiveness of patients after propensity score matching.

EFFICACY	IC group	BC group	p-value
CR	0	0	
PR	47 (45.1%)	25 (24.0%)	
SD	47 (45.1%)	74 (71.2%)	
PD	10 (9.8%)	5 (4.8%)	
ORR	45.1%	24.0%	0.001
DCR	90.2%	95.1%	0.180

BC: Bevacizumab plus chemotherapy; CR: Complete response; DCR: Disease control rate; IC: PD-1 inhibitor plus chemotherapy; ORR: Objective response rate; PD: Progressive disease; PR: Partial response; PD: Progressive disease; SD: Stable disease.

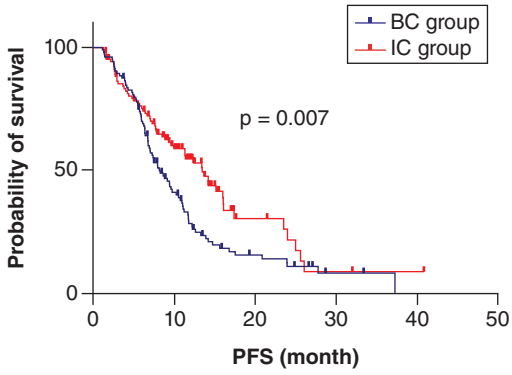

Figure 1. Kaplan–Meier curves of Progression-free survival in patients after Propensity Score Matching.
BC: Bevacizumab plus chemotherapy; IC: PD-1 inhibitor plus chemotherapy; PFS: Progression-free survival.

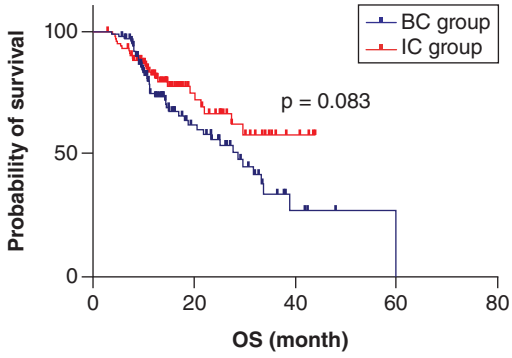

Figure 2. Kaplan–Meier curves of Overall Survival in patients after Propensity Score Matching.
BC: Bevacizumab plus chemotherapy; IC: PD-1 inhibitor plus chemotherapy; OS: Overall survival.

Survival results by PD-L1 expression & molecular subtypes

Stratified analysis of patients who had been tested for PD-L1 expression (45 in the IC group and 33 in the BC group) showed that ORR increased with upregulation of PD-L1 expression in the IC group, with an ORR of 63.6% (14/22) for patients with PD-L1 ≥50% (Table 4). In the PD-L1 ≥50% subgroup and 1–49% subgroup, IC both significantly improved PFS (Figure 3), with 16.2 months (95% CI: 8.9–23.4 months) compared with 6.8 months (95% CI: 6.1–7.5 months) (p = 0.000) in the PD-L1≥1% patients (Figure 4). In the PD-L1 <1% subgroup, PFS was 8.9 months (95% CI: 6.9–10.9 months) and 12.7 months (95% CI: 5.0–20.3 months) in the IC and BC groups, respectively (p = 0.719) (Figure 5).

KRAS mutation status was confirmed in 135 patients (67 in the IC group, 68 in the BC group). PFS of patients with KRAS mutation was longer in the IC group than that in BC group, 16.1 months (95% CI: 6.8–25.4 months) and 6.8 months (95% CI: 3.9–9.7 months), respectively, p = 0.046. The median PFS of patients without KRAS mutations was 13.5 months (95% CI: 8.4–18.5 months) and 8.3 months (95% CI: 6.1–10.5 months) in IC and BC group (p = 0.135) (Figure 3).

TP53 mutation status was recorded in 124 patients (59 in the IC group, 65 in the BC group). In patients with TP53 mutation, the median PFS of IC and BC was 25.1 months (95% CI: 2.8–47.4 months) and 7.4 months (95% CI: 5.6–9.3 months), respectively (p = 0.004). In those patients with wild-type TP53, the median PFS was13.5 months (95% CI: 6.3–20.6 months) and 9.5 months (95% CI: 6.0–12.9 months) (p = 0.585) (Figure 3).

Table 3. Univariate analysis and multivariate analysis of factors associated with progression-free survival in patients after progression-free survival.

	mPFS, month (95% CI)	Univariate analysis		Multivariate analysis	
		HR (95%CI)	p-value	HR (95%CI)	p-value
Sex					
Male	10.8(9.3–12.3)	0.987 (0.684–1.424)	0.945	1.142 (0.673–1.937)	0.622
Female	8.8(6.2–11.5)				
Age					
<65 years	11.0 (9.3–12.7)	1.003 (0.710–1.418)	0.987	0.984 (0.691–1.401)	0.929
≥65 years	9.5 (6.6–12.3)				
ECOG					
0	10.6 (9.1–12.1)	1.085 (0.752–1.565)	0.664	0.954 (0.649–1.403)	0.812
1	8.9 (3.1–14.7)				
Smoking status					
Never	9.2 (7.1–11.3)	0.932 (0.663–1.309)	0.684	1.113 (0.685–1.808)	0.664
Current/former	11.1 (9.1–13.1)				
Brain metastases					
No	11.0 (9.2–12.8)	2.063 (1.289–3.301)	0.003	2.448 (1.463–4.096)	0.001
Yes	7.3 (5.0–9.6)				
Liver metastases					
No	11.1 (9.5–12.7)	1.821 (1.091–3.038)	0.022	1.963 (1.155–3.336)	0.013
Yes	6.8 (5.9–7.7)				
Bone metastases					
No	11.4 (9.3–13.6)	1.542 (1.096–2.169)	0.013	1.688 (1.137–2.507)	0.009
Yes	7.1 (4.8–9.4)				
Stage					
IIIB/IIIC	11.1 (7.3–15.0)	1.027 (0.591–1.785)	0.926	0.695 (0.380–1.273)	0.239
IV	9.7 (7.9–11.4)				
Treatment regimens					
BC	8.2 (6.3–10.1)	0.637 (0.456–0.889)	0.008	0.674 (0.479–0.947)	0.023
IC	13.5 (10.9–16.1)				

HR: Hazard Ratio; PFS: Progression-free survival.

Table 4. Summary of treatment effectiveness in different PD-L1 expression patients.

	ORR	
	IC group	BC group
PD-L1 <1%	30% (3/10)	0% 0/14)
PD-L1 1–49%	61.5% (8/13)	38.5% (5/13)
PD-L1 ≥50%	63.6% (14/22)	16.7% (1/6)
Overall	55.5% (25/45)	18.2% (6/33)

BC: Bevacizumab plus chemotherapy; IC: PD-1 inhibitor plus chemotherapy; ORR: Objective response rate.

Toxicity

Sixteen patients in the IC group had dose reduction or discontinuation because of adverse reactions, including grade 3 nausea and vomiting (3/16), grade 4 leukopenia (1/16), grade 3 anemia (1/16), grade 4 thrombocytopenia (1/16), grade 3 diarrhea (1/16), grade 2 pneumonia (2/16), adrenocortical insufficiency (2/16), immune encephalitis (1/16), immune myocardial injury (1/16), oral mucositis (1/16), capillary hyperplasia (1/16), and hypothyroidism (1/16). In the BC group, 15 patients had drug dose reductions or discontinuation because of adverse reactions, including hemoptysis (1/15), recurrent epistaxis (1/15), grade 3 hypertension (1/15), increased urinary protein (2/15), thrombotic event (1/15), grade 3/4 anemia (5/15), and grade 3/4 thrombocytopenia (4/15).

Discussion

Bevacizumab and ICIs are of great importance for advanced NSCLC with negative driver gene mutations. In clinical practice, most physicians choose ICIs combined with chemotherapy as first-line treatment for patients without contraindications to ICIs, and the use of bevacizumab is declining. However, even in second-line therapy, antiangiogenic drug remains an important agent in combination therapy. In three studies about second-line treatment of advanced non-small cell lung cancer, either bevacizumab, nintedanib, or ramucirumab combined

	Events		HR (95% CI)	mPFS (95% CI)	
	IC group	BC group		IC group	BC group
Sex					
Male	39/73	65/75	0.539 (0.362–0.802)	13.7 (10.9–16.5)	8.0 (5.9–10.2)
Female	20/31	20/29	0.947 (0.507–1.770)	8.9 (2.4–15.4)	8.8 (5.3–12.3)
Age					
<65 y	40/66	55/70	0.815 (0.541–1.229)	11.4 (7.8–11.9)	9.5 (5.8–13.2)
≥65 y	19/38	30/34	0.386 (0.213–0.700)	16.2 (13.2–19.1)	7.5 (6.2–8.8)
ECOG					
0	43/74	61/72	0.688 (0.465–1.109)	12.5 (8.7–16.2)	9.2 (7.0–11.4)
1	16/30	24/32	0.555 (0.292–1.054)	13.5 (12.0–15.0)	6.8 (4.7–8.8)
Smoking status					
Former or current	34/67	57/65	0.534 (0.349–0.818)	13.7 (10.5–16.9)	7.5 (6.3–8.7)
Never	25/37	28/39	0.87 (0.504–1.500)	11.4 (5.8–16.9)	9.2 (7.8–10.6)
EGFR mutation					
No	48/86	74/89	0.629 (0.437–0.907)	13.5 (9.7–17.3)	8.0 (6.4–9.5)
Unknown	11/18	11/15	0.659 (0.283–1.533)	17.4 (3.6–31.3)	11.8 (9.4–14.2)
Brain metastases					
Yes	9/11	12/13	0.976 (0.401–2.372)	7.3 (0.9–13.7)	8.0 (3.6–12.4)
No	50/93	73/91	0.615 (0.428–0.884)	14.3 (10.7–17.9)	8.3 (6.4–10.3)
Liver metastases					
Yes	6/12	11/11	0.409 (0.148–1.134)	7.9 (–)	6.8 (4.8–8.8)
No	53/92	74/93	0.678 (0.476–0.966)	13.5 (10.8–16.2)	9.2 (7.0–11.4)
Bone metastases					
Yes	20/37	34/41	0.709 (0.408–1.233)	8.0 (5.0–10.9)	7.0 (5.8–8.1)
No	39/67	51/63	0.734 (0.473–1.139)	14.3 (11.7–16.9)	8.8 (7.0–10.7)
PD-L1					
PD-L1 <1%	6/10	8/14	1.228 (0.403–2.074)	8.9 (6.9–10.9)	12.7 (5.0–20.3)
PD-L1: 1–49%	5/13	12/13	0.284 (0.089–0.905)	13.5 (1.8–25.0)	8.0 (6.1–9.9)
PD-L1 ≥50%	9/22	5/6	0.081 (0.015–0.403)	16.2 (8.1–24.3)	6.0 (5.1–6.8)
Unknown	39/59	60/71	0.866 (0.577–1.299)	11.4 (6.3–116.4)	8.8 (6.7–11.0)
KRAS mutation					
Yes	14/29	8/11	0.394 (0.158–0.985)	16.1 (6.8–25.4)	6.8 (3.9–9.7)
No	23/38	47/57	0.683 (0.414–1.127)	13.5 (8.4–18.5)	8.3 (6.1–10.5)
Unknown	22/37	30/36	0.752 (0.431–1.312)	13.5 (7.4–19.6)	10.8 (6.3–15.3)
TP53 mutation					
Yes	10/23	22/25	0.334 (0.157–0.711)	25.1 (2.8–47.4)	7.4 (5.6–9.3)
No	21/36	30/40	0.855 (0.486–1.501)	13.5 (6.3–20.6)	9.5 (6.0–12.9)
Unknown	28/45	33/39	0.739 (0.444–1.231)	13.5 (9.0–18.0)	10.5 (5.9–15.3)
Total	50/104	85/104	0.637 (0.465–0.889)	13.5 (10.9–16.1)	8.2 (6.3–10.1)

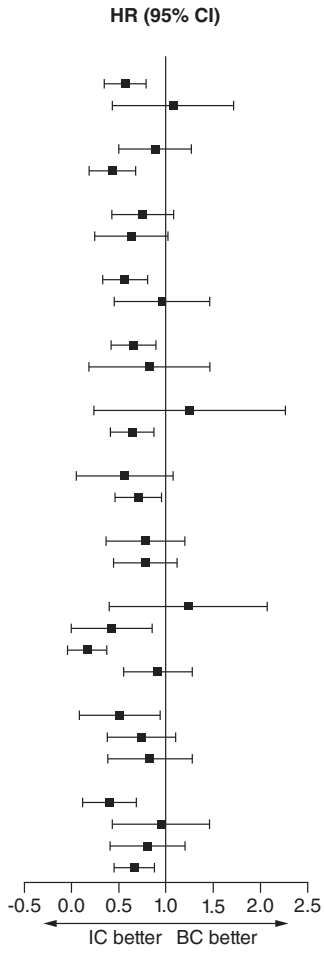

Figure 3. Subgroup analysis of progression-free survival in patients after Propensity Score Matching.
BC: Bevacizumab plus chemotherapy; HR: Hazard ratio; IC: PD-1 inhibitor plus chemotherapy; y: Years.

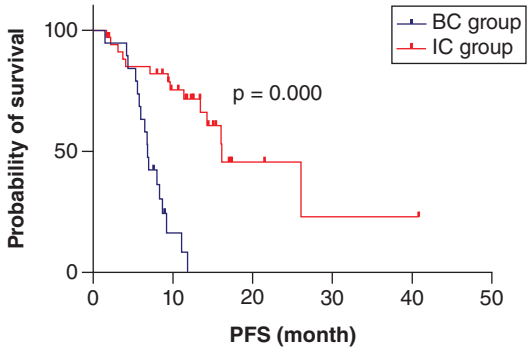

Figure 4. Kaplan–Meier curves of Progression-free survival in PD-L1 ≥1% patients.
BC: Bevacizumab plus chemotherapy; IC: PD-1 inhibitor plus chemotherapy; PFS: Progression-free survival.

with single-agent chemotherapy was superior to mono-chemotherapy [13–15]. Few studies have directly compared ICIs plus chemotherapy with bevacizumab plus chemotherapy. The Impower 150 study [12] compared atezolizumab/carboplatin/paclitaxel and bevacizumab/carboplatin/paclitaxel, the results revealed no significant statistical difference in OS between the two groups. In randomized controlled studies using PD-1-targeted immune checkpoint inhibitors, chemotherapy alone was used as the control. Several meta-analyses have indirectly compared these two regimens, and the conclusions all support that ICI combined with chemotherapy is superior to bevacizumab combined with chemotherapy in both PFS and OS in advanced nsNSCLC without driver gene mutation [16–18]. Our study showed that the IC group showed a significantly improved PFS compared with the BC

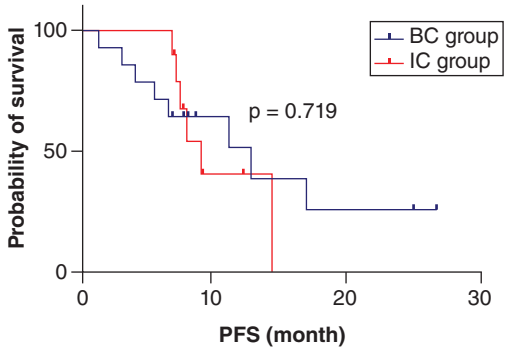

Figure 5. Kaplan–Meier curves of Progression-free survival in PD-L1 <1% patients.
BC: Bevacizumab plus chemotherapy; IC: PD-1 inhibitor plus chemotherapy; PFS: Progression-free survival.

group, and IC regimen was an independent prognostic factor for PFS. Besides, in both randomized studies and clinical practice, the patients in the bevacizumab group are more "selected": non-excavated tumor, no centrally located tumor, no hemoptysis, which could favor the bevacizumab group and therefore reinforce the advantage of the immunotherapy group. But the OS benefit in our study was not significant. This is most likely due to immature OS data, 26/104 (25%) OS end point events were identified in the IC group compared with 43/104 (41.3%) in the BC group.

In our study, brain metastasis, liver metastasis and bone metastasis were independent prognostic factors for PFS. Previous studies have shown that immunotherapy can improve survival in patients with brain metastases, but which remains inferior to that in patients without brain metastases [19]. The incidence of liver metastasis in advanced NSCLC is approximately 4%, and the median survival time of advanced NSCLC patients with liver metastasis is only approximately 4 months [20]. In the KEYNOTE189 study, pembrolizumab combined with chemotherapy versus chemotherapy significantly prolonged median OS in patients with liver metastases (12.6 months vs 6.6 months, $p < 0.001$), but that was lower compared with patients without liver metastases (23.7 months vs 13.2 months) [21]. Nivolumab as second-line therapy for advanced NSCLC significantly improved OS in patients with liver metastases compared with docetaxel (6.8 months vs 5.9 months, HR = 0.68; 95% CI: 0.50–0.91), but the difference was minor and still lower than that in the overall population [22]. However, several meta-analyses showed that ICI plus chemotherapy was comparable or inferior to bevacizumab plus chemotherapy in patients with liver metastases [17,18,23]. Previous studies have suggested that immunotherapy is less effective in patients with liver metastases, and this is mainly associated with the immunosuppressive microenvironment in liver. The liver is the major organ of metabolism, and chronic exposure to large amounts of foreign antigens requires the development of immune tolerance to these antigens to maintain immune homeostasis [20]. Yu *et al.* found that liver metastases siphon activated $CD8^+$ T cells from the systemic circulation in mouse models. Fas^+CD8^+ T cells interact with $FasL^+CD11b^+F4/80^+$ monocyte-derived macrophages and then undergo apoptosis, leading to a systemic immune desert. The authors also found that the peripheral T cell numbers and tumoral T cell diversity and function of NSCLC with liver metastases diminished [24]. The vascular remodeling and immunomodulatory effects of bevacizumab can result in immune reprogramming of the tumor microenvironment from an immunosuppressive to an immune-permissive state [25], which may make bevacizumab a more effective treatment option than ICIs for patients with liver metastases.

Bone metastasis most commonly occurs in advanced lung cancer, especially in patients with lung adenocarcinoma, with an incidence of approximately 30–60% [26]. Bone metastasis confers a poor prognosis [27,28], which is partly associated with the presence of bone-related events [28]. Bone-targeting agents, such as bisphosphonates, combined with systemic antineoplastic therapy can improve survival and delay the occurrence of bone-related events in patients with bone metastases. Most phase III randomized studies exclude patients who have or are at high risk for bone-related events, so these patients are not adequately studied. However, these patients account for a large part of patients in real-world studies. A retrospective study that included 1579 patients with NSCLC showed that the ORR, PFS and OS were lower in patients with bone metastases than in those without bone metastases [29], and our study is consistent with this conclusion.

We performed subgroup analysis for patients that were tested for PD-L1 expression. The response rate increased with upregulation of PD-L1 expression in the IC group, which is consistent with previous studies [30]. In the BC group, the highest ORR was observed in patients with PD-L1 of 1%–49%, possibly because BC treatment response was not related to PD-L1 expression. In addition, among patients with PD-L1 $\geq$1%, PFS in the IC group was

significantly longer that in than in BC group, while among those with PD-L1 <1%, no significant difference was observed. Some meta-analyses have also shown that ICI plus chemotherapy is not superior to bevacizumab plus chemotherapy for patients with PD-L1 <1% [16,23]. However, the number of patients in our study with tested PD-L1 expression was small, and OS data were immature, therefore, these conclusions need to be further validated.

KRAS mutation is one of the most common mutations in lung cancer patients with adenocarcinoma, with an incidence of approximately 10–15% in Asian patients [31]. TP53 mutation is also a common mutation in lung cancer patients and often coexists with KRAS mutation. Patients with KRAS and/or TP53 mutations respond better to ICIs than patients without these mutations [31,32]. The possible mechanisms may be that KRAS and/or TP53 mutations can increase PD-L1 expression, promote immune cell infiltration, and increase tumor mutation burden [33–36]. Similar results were observed in our study.

Our study has some limitations. The study was a retrospective study based on real-world data, which was obtained from electronic medical records and part of it could not verify their accuracy. Besides, iRECIST [37] criteria was used in some cases, especially for the judgment of progression disease. As a result, the response assessment criteria may be inconsistent, leading to potential misclassification. In addition, PSM can only balance some observed factors, and may ignore some unmeasured confounders that may have an impact on both the outcome and intervention variables. Given the incomplete documentation of adverse reactions in electronic medical records and recall bias, toxicities were not evaluated in detail. Additionally, OS data are not mature, and the mutation status of some patients was unclear, which may lead to differences in statistical results. Only a small portion of the patients had tested PD-L1 expression, and our results should be further validated in a larger sample size.

Conclusion

Anti-PD-1 ICI plus chemotherapy was superior to bevacizumab plus chemotherapy as first-line treatment for advanced nsNSCLC with negative driver gene mutation, maybe more significant in those patients with high PD-L1 expression or KRAS or TP53 mutations. For patients with PD-L1 <1%, the superiority of ICI plus chemotherapy over bevacizumab plus chemotherapy should be further validated.

Summary points

- Currently, most of clinical studies on first-line immunotherapy for advanced non-squamous non-small cell lung cancer (nsNSCLC) compared PD-1 inhibitor plus chemotherapy with chemotherapy alone, and confirmed that the former is superior to the latter. Bevacizumab combined with chemotherapy has also been proven to be better than chemotherapy alone for advanced nsNSCLC. But it is not clear whether PD-1 inhibitor combined with chemotherapy is better than bevacizumab combined with chemotherapy.
- In this retrospective study, we directly compared the effectiveness of PD-1 inhibitor combined with chemotherapy and bevacizumab combined with chemotherapy in advanced nsNSCLC, confirming the superiority of the former in the overall population.
- However, we did not observe the advantage of PD-1 inhibitor plus chemotherapy in patients with PD-L1 <1%.
- Prospective data are required to further confirm the efficacy of the two treatment options in advanced nsNSCLC with PD-L1 <1%, so as to determine the most appropriate treatment regimen for these patients.

Author contributions

J Wang: data collection, investigation, data analysis and interpretation, methodology, writing – original draft, writing – review and editing. Qin Chen: data collection, investigation, writing – review and editing. Xinyue Wang: data collection, investigation, writing – review and editing. Dingzhi Huang: conceptualization, methodology, writing – review and editing. Richeng Jiang: conceptualization, investigation, supervision, methodology, writing – review and editing.

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No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

This study was approved by the medical ethics committee of Tianjin Medical University Cancer Institute & Hospital, National Clinical Research Center for Cancer (no. bc2022179). All procedures in this study that involved human participants were performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or with comparable ethical standards.

Data sharing statement

The authors certify that this manuscript reports original clinical trial data. Individual, de-identified participant data that underlie the results reported in this article (text, tables, figures and appendices) are available from the corresponding author following publication, including the clinical study report and study protocol.

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