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A Combined Biomarker of Peripheral PD-1$^+$ T Cells and Tumor PD-L1 Guides First-Line Treatment Selection in NSCLC: A Prospective Cohort Study

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Abstract

Background

Selecting first-line therapy for advanced non-small cell lung cancer (NSCLC) without driver mutations is challenging due to a lack of predictive biomarkers. Tumor PD-L1 testing is invasive, heterogeneous, and imperfect for identifying patients at risk of hyperprogression. We investigated non-invasive biomarkers to guide treatment choice between chemo-immunotherapy and chemo-antiangiogenic therapy.

Methods

This prospective cohort study enrolled 66 treatment-naïve patients with metastatic NSCLC. Patients received either first-line chemo-immunotherapy (n = 37) or chemo-antiangiogenic therapy (n = 29). We compared progression-free survival (PFS), overall survival (OS), and objective response rate (ORR). The predictive value of tumor PD-L1 expression combined with PD-1 expression on peripheral blood CD4 + and CD8 + T cells was assessed.

Results

No significant differences were found between the two treatment groups in median PFS (7.9 vs. 9.2 months, P = 0.357), OS (20.8 vs. 19.8 months, P = 0.616), or ORR (32.4% vs. 41.4%, P = 0.623). However, within the chemo-immunotherapy group, patients with high PD-L1 and/or high PD-1 on CD4+/CD8 + T cells had significantly superior PFS (HR 0.18, P = 0.006) and OS. In the chemo-antiangiogenic group, low PD-1 on CD4 + T cells predicted better survival (mOS: 24.9 vs. 9.3 months, P = 0.032). Adverse events were comparable.

Conclusion

First-line chemo-immunotherapy and chemo-antiangiogenic therapy showed comparable efficacy in an unselected population. A composite biomarker of peripheral PD-1 + T cells and tumor PD-L1 effectively identified patients with superior survival benefits from immunotherapy, offering a promising non-invasive strategy for personalizing initial NSCLC treatment.

Introduction

Non-small cell lung cancer (NSCLC) is the predominant type of malignant lung tumor, with most patients diagnosed at an advanced stage and facing a poor prognosis[1]. The advent of immune checkpoint inhibitors (ICIs) targeting programmed death-1 (PD-1) or its ligand (PD-L1) axis has significantly transformed the treatment landscape for advanced NSCLC without actionable driver mutations [2–6]. Single or combinations of ICIs with chemotherapy have demonstrated superior survival outcomes,

establishing this approach as a standard of care [7–18].Parallel to this, the integration of anti-angiogenic agents, such as bevacizumab, with chemotherapy has also shown significant survival benefits and remains a cornerstone of treatment, particularly for non-squamous NSCLC [19–21].

This expansion of first-line options, while beneficial, presents a critical clinical dilemma: how to choose the most effective initial therapy for an individual patient? Although meta-analyses suggest a superiority of immuno-chemotherapy over antiangiogenic-chemotherapy in non-squamous NSCLC, such indirect comparisons have inherent limitations, lack of biomarkers guiding, more importantly, profound interpatient heterogeneity exists [22–25]. A significant proportion of patients derive limited or no benefit from ICIs, with some experiencing rapid disease progression, a phenomenon termed hyperprogression [26, 27].

Currently, tumor PD-L1 expression is currently a biomarker widely used to guide clinical practice, but it has considerable limitations [26, 28, 29]. Its assessment requires invasive tumor biopsies, which are not always feasible and are subject to spatial and temporal heterogeneity. Furthermore, PD-L1 expression is an imperfect predictor, as some patients with high PD-L1 do not respond to immunotherapy, while others with low expression may benefit [30]. Beyond the intrinsic characteristics of tumor cells, the status of the host immune system, particularly the critical roles of T cells and macrophages in anti-tumor immunity, also significantly influences treatment effects [31]. Peripheral blood, as a liquid biopsy, offers a promising alternative. The expression of PD-1 on circulating T cells reflects the systemic immune status and may capture the dynamics of the host anti-tumor immune response [32]. We hypothesize that combining the assessment of the local tumor microenvironment (via PD-L1) with the systemic immune status (via peripheral blood PD-1^+ T cells) could yield a more comprehensive and clinically practical biomarker.

This prospective cohort study aims to directly compare the efficacy of first-line immuno-chemotherapy versus antiangiogenic-chemotherapy in patients with advanced, driver mutation-negative NSCLC and to evaluate whether a combined biomarker panel, incorporating tumor PD-L1 and peripheral blood PD-1 expression on $CD4^+$ and $CD8^+$ T cells, could effectively identify patients most likely to benefit from one treatment strategy over the other.

Methods

Study Design

This prospective cohort study screened patients diagnosed with driver gene-negative advanced NSCLC at Beijing Chest Hospital, Capital Medical University (Beijing, China) between November 2017 and August 2020. Eligible patients had received at least one cycle of chemotherapy combined with either immunotherapy or anti-angiogenic therapy. The inclusion and exclusion criteria were as follows: age ≥ 18 years; at least one baseline measurable lesion assessed per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1; relatively stable performance status; unresectable stage III or IV NSCLC

defined by the 8th edition of the TNM classification for lung cancer; and absence of genomic alterations such as EGFR or ALK, as confirmed by next-generation sequencing (NGS) or amplification refractory mutation system polymerase chain reaction (ARMS-PCR). Patient enrollment and treatment were conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Beijing Chest Hospital, Capital Medical University (Approval No.: KY-2018-002). All patients provided written informed consent before treatment initiation.

Treatment and Follow-up

Enrolled patients received 4–6 cycles of chemotherapy followed by either immunotherapy or anti-angiogenic therapy, leading to their classification into two groups: the immuno-chemotherapy combination group and the anti-angiogenic-chemotherapy combination group. Immunotherapy involved Sintilimab (Innovent Biologics, China) or Toripalimab (Junshi Biosciences, China). The anti-angiogenic agent used was Bevacizumab. Chemotherapy regimens included platinum-based drugs combined with pemetrexed, nab-paclitaxel, or gemcitabine. The actual treatment administered was determined jointly by the physician and the patient based on the patient's physical condition and preferences. Immunotherapy was continued until disease progression or the occurrence of unacceptable toxicity.

Tumor response was regularly evaluated according to RECIST 1.1 criteria after treatment initiation, and patient death and progression status were recorded. OS was defined as the time from treatment initiation to death from any cause or the last follow-up. PFS was recorded until disease progression, patient death, or the last follow-up date, which was December 2022. Adverse events (AEs) were assessed according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.

Data Collection

Patient tissue specimens were collected. Tumor tissue sections were stained using immunohistochemistry (IHC) with the 22C3 antibody. Two pathologists examined the staining under a microscope and calculated the percentage of tumor cells showing membranous PD-L1 staining (Tumor Proportion Score, TPS). Any discrepancies in PD-L1 assessment were resolved by a third, experienced pathologist. Based on the TPS, samples were categorized into a negative group (PD-L1 < 1%) and a positive group (PD-L1 ≥ 1%). Additionally, peripheral blood samples were collected from patients before treatment. Peripheral blood mononuclear cells (PBMCs) were isolated, and the expression of PD-1 on the surface of CD8-positive and CD4-positive T cells was detected using flow cytometry. The proportion of PD-1-positive cells was calculated.

Statistical Analysis

Statistical analyses were performed using R software (version 4.4.1). A P-value < 0.05 was considered statistically significant. Categorical variables were compared using Fisher's exact test or Pearson's chi-square test, while continuous variables were compared using the Mann-Whitney U test. Median OS and PFS were calculated using the Kaplan-Meier method, and survival differences between groups were compared using the log-rank test. Univariate and multivariate Cox regression analyses were employed to identify significant prognostic factors associated with survival.

Results

Patient Characteristics

By August 2020, 66 patients with driver gene-negative advanced NSCLC who received chemotherapy combined with either immunotherapy or anti-angiogenic therapy were enrolled (Fig. 1). The median age was 63.5 years (range: 58–68), with 57 (86.4%) males and 9 (13.6%) females. The predominant pathological types were lung adenocarcinoma (n = 43, 65.2%) and squamous cell carcinoma (n = 21, 31.8%). Most patients had lymph node metastasis (n = 58, 89.4%) and distant metastasis (n = 57, 86.4%), and a high proportion had a history of or current smoking (n = 55, 83.3%). Based on the first-line regimen, patients were divided into a chemo-immunotherapy group (n = 37; Sintilimab, n = 18; Toripalimab, n = 19) and a chemo-antiangiogenic therapy group (n = 29; all Bevacizumab). Except for a higher proportion of squamous cell carcinoma in the chemo-immunotherapy group, other baseline characteristics were balanced between the two groups (Table 1).

Table 1
Baseline characteristics by treatment group for non-small cell lung cancer patients

Characteristics	Overall (N = 66)	AAT + Che (N = 29)	IO + Che (N = 37)	P
Gender, n (%)				0.2932
female	9 (13.6)	2 (6.9)	7 (18.9)	
male	57 (86.4)	27 (93.1)	30 (81.1)	
Age, years	63.5 [58.0, 68.0]	65.0 [56.0, 68.0]	63.0 [58.0, 68.0]	0.9948
Medication cycles, cycles	9.0 [4.2, 13.8]	10.0 [6.0, 14.0]	8.0 [4.0, 12.0]	0.1999
Pathology, n (%)				0.0019
LUAD	43 (65.2)	24 (82.8)	19 (51.4)	
LUSC	21 (31.8)	3 (10.3)	18 (48.6)	
other	2 (3.0)	2 (6.9)	0 (0.0)	
Liver metastases, n (%)	6 (9.1)	2 (6.9)	4 (10.8)	0.9064
Bone metastases, n (%)	20 (30.3)	9 (31.0)	11 (29.7)	1
Brain metastases, n (%)	2 (3.0)	0 (0.0)	2 (5.4)	0.5837
Adrenal metastases, n (%)	7 (10.6)	2 (6.9)	5 (13.5)	0.6428
Pleural metastases, n (%)	19 (28.8)	5 (17.2)	14 (37.8)	0.1187
Lung metastases, n (%)	22 (33.3)	9 (31.0)	13 (35.1)	0.9301
T, n (%)				0.189
T1	7 (10.6)	5 (17.2)	2 (5.4)	
T2	18 (27.3)	10 (34.5)	8 (21.6)	
T3	8 (12.1)	3 (10.3)	5 (13.5)	
T4	33 (50.0)	11 (37.9)	22 (59.5)	
N, n (%)				0.8574
N0	8 (12.1)	4 (13.8)	4 (10.8)	
N1	4 (6.1)	1 (3.4)	3 (8.1)	

AAT, Anti-angiogenic therapy; Che, chemotherapy; IO, immunotherapy; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; PDL1, programmed cell death-ligand 1; PD1, Programmed cell death protein 1.

Characteristics	Overall (N = 66)	AAT + Che (N = 29)	IO + Che (N = 37)	P
N2	26 (39.4)	12 (41.4)	14 (37.8)	
N3	28 (42.4)	12 (41.4)	16 (43.2)	
M, n (%)				0.6934
M0	9 (13.6)	5 (17.2)	4 (10.8)	
M1	57 (86.4)	24 (82.8)	33 (89.2)	
Smoking status, n (%)				0.4092
current	42 (63.6)	19 (65.5)	23 (62.2)	
former	13 (19.7)	7 (24.1)	6 (16.2)	
never	11 (16.7)	3 (10.3)	8 (21.6)	
PDL1, n (%)				1
high	45 (72.6)	18 (72.0)	27 (73.0)	
low	17 (27.4)	7 (28.0)	10 (27.0)	
CD4-PD1, n (%)				1
high	14 (46.7)	6 (46.2)	8 (47.1)	
low	16 (53.3)	7 (53.8)	9 (52.9)	
CD8-PD1, n (%)				0.6295
high	9 (30.0)	5 (38.5)	4 (23.5)	
low	21 (70.0)	8 (61.5)	13 (76.5)	
CD4-PD1/PDL1 high, n (%)				0.1888
no	5 (9.3)	0 (0.0)	5 (14.7)	
yes	49 (90.7)	20 (100.0)	29 (85.3)	
CD4-PD1/PDL1 low, n (%)				1
yes	17 (63.0)	6 (60.0)	11 (64.7)	
no	10 (37.0)	4 (40.0)	6 (35.3)	
CD8-PD1/PDL1 high, n (%)				0.3112

AAT, Anti-angiogenic therapy; Che, chemotherapy; IO, immunotherapy; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; PDL1, programmed cell death-ligand 1; PD1, Programmed cell death protein 1.

Characteristics	Overall (N = 66)	AAT + Che (N = 29)	IO + Che (N = 37)	P
no	4 (7.5)	0 (0.0)	4 (11.8)	
yes	49 (92.5)	19 (100.0)	30 (88.2)	
CD8-PD1/PDL1 low, n (%)				0.0909
yes	22 (81.5)	6 (60.0)	16 (94.1)	
no	5 (18.5)	4 (40.0)	1 (5.9)	
CD4-PD1/CD8-PD1 high, n (%)				0.8215
no	12 (40.0)	6 (46.2)	6 (35.3)	
yes	18 (60.0)	7 (53.8)	11 (64.7)	
CD4-PD1/CD8-PD1 low, n (%)				0.1874
yes	25 (83.3)	9 (69.2)	16 (94.1)	
no	5 (16.7)	4 (30.8)	1 (5.9)	
CD4-PD1/CD8-PD1/PDL1 high, n (%)				0.4522
no	3 (5.6)	0 (0.0)	3 (8.8)	
yes	51 (94.4)	20 (100.0)	31 (91.2)	

AAT, Anti-angiogenic therapy; Che, chemotherapy; IO, immunotherapy; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; PDL1, programmed cell death-ligand 1; PD1, Programmed cell death protein 1.

Table 1 also details patient baseline characteristics, tumor cell PD-L1 expression, and lymphocyte PD-1 expression. Among the 62 patients with evaluable PD-L1 results, 45 (72.6%) were positive and 17 (27.4%) were negative. Flow cytometry was used to assess the percentage of PD-1 expression on baseline peripheral blood $CD4^+$ and $CD8^+$ T cells in 30 patients, who were then dichotomized into high and low expression groups using a 30% cutoff. Results showed 14 (46.7%) patients had high CD4-PD1 expression, while 9 (30.0%) had high CD8-PD1 expression.

Survival Analysis

By December 2022, disease progression had occurred in 62 patients, and 48 deaths were recorded in the overall population. The median PFS and OS were 7.9 months (95% CI: 7.3–10.8) and 19.9 months (95% CI: 17.9–23.7), respectively. In the chemo-immunotherapy and chemo-antiangiogenic groups, the mPFS was 7.9 months (95% CI: 6.7–11.7) vs. 9.2 months (95% CI: 7.3–11.0), and mOS was 20.8 months (95% CI: 13.9–28.5) vs. 19.8 months (95% CI: 18.5–24.9). No statistically significant differences in PFS (HR:

0.79, 95% CI: 0.48–1.31, P = 0.357) or OS (HR: 0.86, 95% CI: 0.49–1.53, P = 0.616) were observed between the two groups (Fig. 2A-B). Univariate Cox regression analysis for PFS in the entire cohort indicated that sex (HR: 0.5, 95% CI: 0.24–1.05, P = 0.067), brain metastasis (HR: 3.59, 95% CI: 0.83–15.55, P = 0.087), and PD-L1 expression (HR: 0.49, 95% CI: 0.27–0.9, P = 0.022) were associated with disease progression in NSCLC patients (**Supplementary Table 1**).

Subgroup survival analyses for PFS and OS were performed based on PD-L1, CD4-PD1, and CD8-PD1 expression within each treatment cohort. In the chemo-immunotherapy group, PD-L1 positive patients had significantly longer PFS than PD-L1 negative patients (10.8 vs. 7.1 months, P = 0.018), although the difference in OS (21.9 vs. 14.8 months, P = 0.182) was not statistically significant. Differences in clinical outcomes based on CD4-PD1 expression (mPFS: 13.8 vs. 6.7 months, P = 0.079; mOS: 23.1 vs. 13.9 months, P = 0.482) and CD8-PD1 expression (mPFS: 7.7 vs. 7.3 months, P = 0.991; mOS: 24.6 vs. 18.0 months, P = 0.198) did not reach statistical significance. In the chemo-antiangiogenic group, higher CD4-PD1 expression was associated with worse clinical outcomes for OS (mOS: 9.3 vs. 24.9 months, P = 0.032). Survival was comparable between different PD-L1 expression levels (mPFS: 8.3 vs. 7.7 months, P = 0.579; mOS: 18.5 vs. 21.5 months, P = 0.718). No significant associations with prognosis were observed for CD4-PD1 (mPFS: 8.1 vs. 11.6 months, P = 0.196) or CD8-PD1 expression (mPFS: 9.2 vs. 12.5 months, P = 0.221; mOS: 10.3 vs. 21.2 months, P = 0.206) (Fig. 2C-H).

To explore more precise treatment guidance, combinations of the above biomarkers were investigated. Regarding PFS in the chemo-immunotherapy cohort (Fig. 3A-B), patients with high expression of either PD-L1 or CD4-PD1 (HR: 0.32, 95% CI: 0.11–0.90, P = 0.030), high expression of either PD-L1 or CD8-PD1 (HR: 0.18, 95% CI: 0.05–0.60, P = 0.006), high expression of either CD4-PD1 or CD8-PD1 (HR: 0.22, 95% CI: 0.06–0.73, P = 0.014), or high expression of any one of the three markers (HR: 0.18, 95% CI: 0.05–0.69, P = 0.012) had significantly better PFS (Fig. 3C-F). Similarly, longer OS was observed in patients with high expression of either PD-L1 or CD4-PD1 (HR: 0.38, 95% CI: 0.14–1.06, P = 0.065), high expression of either PD-L1 or CD8-PD1 (HR: 0.28, 95% CI: 0.09–0.91, P = 0.035), high expression of either CD4-PD1 or CD8-PD1 (HR: 0.33, 95% CI: 0.10–1.12, P = 0.074), or high expression of any one of the three markers (HR: 0.25, 95% CI: 0.07–0.92, P = 0.038) (Fig. 3G-J).

In the chemo-antiangiogenic cohort (Fig. 4A-B), patients with low expression of either PD-L1 or CD4-PD1 had a slower disease progression rate (HR: 9.66, 95% CI: 1.04–89.85, P = 0.046). Differences were not statistically significant for low expression of either PD-L1 or CD8-PD1 (HR: 3.95, 95% CI: 0.70-22.13, P = 0.118), or low expression of either CD4-PD1 or CD8-PD1 (HR: 1.91, 95% CI: 0.55–6.66, P = 0.310) (Fig. 4C-E). For OS, patients with low expression of either PD-L1 or CD4-PD1 (HR: 8.95, 95% CI: 0.95–84.31, P = 0.056), low expression of either PD-L1 or CD8-PD1 (HR: 2.09, 95% CI: 0.51–8.56, P = 0.303), or low expression of either CD4-PD1 or CD8-PD1 (HR: 3.70, 95% CI: 0.90-15.27, P = 0.070) tended to have better prognosis, but the differences did not reach significance (Fig. 4F-H).

Treatment Response

No significant differences in ORR (32.4% [12/37] vs. 41.4% [12/29], P = 0.623) or DCR (75.7% [28/37] vs. 86.2% [25/29], P = 0.45) were observed between first-line chemo-immunotherapy and first-line chemo-antiangiogenic therapy in driver gene-negative NSCLC patients. **Supplementary Table 2** compares ORR and DCR across different biomarker subgroups, revealing predictive value for short-term treatment efficacy. In the chemo-immunotherapy group, the PD-L1 high expression group had numerically higher ORR (40.74% [11/27] vs. 10.00% [1/10], P = 0.168) and DCR (81.48% [22/27] vs. 60.00% [6/10], P = 0.357) than the PD-L1 low expression group, but the differences were not statistically significant. Consistent results were found in subgroups defined by CD4-PD1 or PD-L1, CD8-PD1 or PD-L1, and CD4/CD8-PD1 or PD-L1. In the chemo-antiangiogenic group, patients with low CD4-PD1 expression had a slightly higher ORR (71.43% [5/7] vs. 33.33% [2/6], P = 0.415).

Safety Analysis

Table 2 summarizes the incidence of AEs. Most patients experienced treatment-related AEs. The incidence of any-grade AEs (86.2% vs. 89.2%) and grade ≥ 3 AEs (65.5% vs. 67.6%) was comparable between the chemo-antiangiogenic and chemo-immunotherapy groups. In the chemo-antiangiogenic group, the most frequent any-grade AEs were anemia, neutropenia, leukopenia, limb numbness, nausea, thrombocytopenia, and pain. In the chemo-immunotherapy group, common any-grade AEs included anemia, neutropenia, leukopenia, thrombocytopenia, nausea, and increased alanine aminotransferase. The most common grade ≥ 3 AE in both groups was neutropenia. Additionally, in the chemo-immunotherapy cohort, 23 (62.2%) patients experienced immune-related AEs, the most frequent being hypothyroidism (24.3%), immune-mediated pneumonitis (13.5%), and hyperthyroidism (8.1%). Notably, AEs led to treatment discontinuation in 15 (51.7%) patients in the chemo-antiangiogenic group and 19 (51.4%) patients in the chemo-immunotherapy group.

Table 2
Post-treatment adverse events in patients with non-small cell lung cancer by treatment group

Event	AAT+Che N = 29			IO+Che N = 37		
	All Grade	≥Grade 3	SAE	All Grade	≥Grade 3	SAE
Any event	25(86.2)	19(65.5)	7(24.1)	33(89.2)	25(67.6)	16(43.2)
Anemia	18(62.1)	3(10.3)	0	30(81.1)	8(21.6)	1(2.7)
Decreased neutrophil count	19(65.5)	15(51.7)	3(10.3)	26(70.3)	15(40.5)	2(5.4)
Decreased white blood count	16(55.2)	6(20.7)	3(10.3)	24(64.9)	8(21.6)	2(5.4)
Decreased platelet	9(31.0)	4(13.8)	1(3.4)	19(51.4)	8(21.6)	5(13.5)
Nausea	12(41.4)	1(3.4)	0	12(32.4)	0	0
Increased alanine aminotransferase	5(17.2)	0	0	14(37.8)	0	0
Ache	9(31.0)	0	0	8(21.6)	0	0
Asthenia	8(27.6)	0	0	9(24.3)	0	0
Numbness of the limbs	13(44.8)	0	0	2(5.4)	0	0
Vomiting	6(20.7)	1(3.4)	0	7(18.9)	0	0
Hypoalbuminemia	2(6.9)	0	0	11(29.7)	0	0
Increased aspartate aminotransferase	2(6.9)	0	0	10(27.0)	1(2.7)	0
Constipation	3(10.3)	0	0	8(21.6)	0	0
Proteinuria	8(27.6)	0	0	2(5.4)	0	0
Pyrexia	1(3.4)	0	0	9(24.3)	0	0
Lung infection	5(17.2)	3(10.3)	3(10.3)	7(18.9)	6(16.2)	4(10.8)
Diarrhea	3(10.3)	1(3.4)	0	6(16.2)	0	0
Hypothyroidism	0	0	0	9(24.3)	0	0
Insomnia	5(17.2)	0	0	4(10.8)	0	0
Decreased appetite	3(10.3)	0	0	6(16.2)	0	0

AAT, Anti-angiogenic therapy; Che, chemotherapy; IO, immunotherapy.

Event	AAT+Che N = 29			IO+Che N = 37		
	All Grade	≥Grade 3	SAE	All Grade	≥Grade 3	SAE
Hypertention	5(17.2)	1(3.4)	0	2(5.4)	1(2.7)	0
Hemoptysis	2(6.9)	0	0	5(13.5)	0	1(2.7)
Dysfunction of blood coagulation	1(3.4)	0	0	7(18.9)	1(2.7)	0
Dysphagia	3(10.3)	0	0	4(10.8)	0	0
Baldness	7(24.1)	0	0	0(0.0)	0	0
Hyponatremia	2(6.9)	0	0	4(10.8)	3(8.1)	1(2.7)
Immune pneumonitis	1	0	0	5(13.5)	0	0
Epistaxis	3(10.3)	1(3.4)	0	2(5.4)	0	0
Hypokalemia	0	0	0	5(13.5)	1(2.7)	0
Hypochloremia	1(3.4)	0	0	4(10.8)	2(5.4)	1(2.7)
Decreased weight	3(10.3)	0	0	2(5.4)	0	0
Dizziness	3(10.3)	0	0	2(5.4)	0	0

AAT, Anti-angiogenic therapy; Che, chemotherapy; IO, immunotherapy.

Discussion

Both immunotherapy and anti-angiogenic therapy combined with chemotherapy are recommended as first-line treatment options for patients with advanced NSCLC[2, 19–21]. In this prospective cohort study of patients with driver-negative advanced NSCLC, we found that first-line chemo-immunotherapy and chemo-antiangiogenic therapy yielded comparable efficacy in the overall population. However, leveraging a novel combined biomarkers approach, we identified distinct patient subgroups derived differential survival benefits from each regimen. Specifically, patients exhibiting high PD-L1 expression and/or high PD-1 expression on peripheral $CD4^+$/$CD8^+$ T cells achieved significantly improved outcomes with immunotherapy. Conversely, patients with low PD-1 expression on $CD4^+$ T cells appeared to be associated with a more favorable prognosis with anti-angiogenic therapy.

Our findings align with the known predictive value of PD-L1 for ICI efficacy but also highlight its inadequacy as a standalone biomarker[30]. The inability of PD-L1 to identify all responders and the risk of hyperprogression underscore the complexity of the tumor-immune interaction[30]. In the context of immunotherapy, the expression of T immune cells and their molecular markers are potential targets for

reactivation by immunotherapies. Tumor-infiltrating lymphocytes (TILs) within the tumor tissue or T cells in the peripheral blood are increasingly gaining attention. $CD8^+$ TILs are spatially co-localized with PD-1/PD-L1, and their high infiltration density can predict the efficacy of anti-PD-1/PD-L1 therapy[33–35]. A meta-analysis incorporating 33 studies demonstrated that high levels of $CD8^+$ TILs are associated with improved OS and PFS in cancer patients receiving immunotherapy[36]. Furthermore, the expression of immune checkpoint receptors on immune cells may play a critical role. Patients with higher PD-L1 levels in tumor-associated macrophages often exhibit increased $CD8^+$ T cell infiltration[37]. TCR clones expanded from $PD\text{-}1^+CD8^+$ TIL populations can recognize autologous tumors, indicating that PD-1 expression on $CD8^+$ T cells serves as a potential biomarker for immunotherapy[38, 39]. As immunosuppressive cells, regulatory T cells (Tregs) see their suppressive function enhanced by PD-1 expression, while PD-1 expression on effector $CD8^+$ T cells inhibits their tumor-killing capacity. Consequently, the ratio of $PD\text{-}1^+CD8^+$ T cells to $PD\text{-}1^+$Tregs demonstrates superior predictive power for response to PD-1 blockade therapy compared to traditional PD-L1 expression alone[40]. Our data suggest that the systemic immune context, as gauged by circulating $PD\text{-}1^+$ T cells, provides complementary information. This is biologically plausible, as circulating $PD\text{-}1^+$ $CD8^+$ T cells can share tumor antigen specificity with their intratumoral counterparts and may represent a mobilized, tumor-reactive T cell pool[32, 36]. Moreover, the predictive power of the $PD\text{-}1^+IFN\text{-}\gamma^+$ subset among circulating $CD8^+$ T cells further supports the relevance of functional subsets within the peripheral $PD\text{-}1^+$ compartment in NSCLC patients receiving immuochemotherapy [41].

Conversely, the association between *low* CD4-PD1 and better outcomes with anti-angiogenic therapy is intriguing. We postulate that bevacizumab may be more effective in a less chronically activated or exhausted systemic immune environment, a hypothesis that warrants further investigation. $CD4^+$ T cells play a core role in anti-tumor immunity by assisting in the activation of $CD8^+$ T cells within lymph nodes and facilitating their migration to the tumor microenvironment[42]. Our finding that high PD-1 on $CD4^+$ T cells predicts ICI benefit resonates with studies showing that $PD\text{-}1^+$ $CD4^+$ T cells in tumors can be reactivated by PD-1 blockade to help orchestrate anti-tumor immunity. A meta-analysis incorporating 13 studies showed that high levels of $CD4^+$ T cells in tumor tissue were associated with a better ORR, while the level of $CD4^+$ T cells in peripheral blood could predict patients' PFS[43]. Studies have found that $CD4^+$ TIL populations defined by high expression of PD-1 and CD39 are prone to exhaustion, and in vitro PD-1 blockade can activate $CD4^+$ T cells, thereby promoting the proliferation of tumor-specific $CD8^+$ T cells[44, 45]. In NSCLC patients receiving anti-PD-1/PD-L1 therapy, responders exhibit a more significant expansion of PD-1-positive memory $CD4^+$ T cells compared to non-responders, providing direction for biomarker exploration[46].

The single metric of tumor tissue PD-L1 expression is insufficient to elucidate the complex effects of immunotherapy. Furthermore, bevacizumab combined with chemotherapy promotes vascular normalization, leading to increased infiltration of $CD8^+$ T cells exhibiting phenotypes such as high PD-1 expression[47, 48]. This provides a rationale for combining anti-angiogenic therapy with

immunotherapy[26, 49]. The most significant implication of our study is the proposition of a practical, "treatment selection algorithm" at the point of diagnosis. For patients with driver-negative advanced NSCLC, initial assessment could include both tumor PD-L1 testing (if tissue is available) and a simple peripheral blood flow cytometry for PD-1 on T cells. Patients classified as "combined biomarker high" (PD-L1^{high} *and/or* CD4/CD8-PD1^{high}) would be strong candidates for first-line immuno-chemotherapy. Those classified as "combined biomarker low," particularly with CD4-PD1^{low}, might be more appropriately directed towards chemo-antiangiogenic therapy, potentially sparing them the cost and toxicity of ineffective immunotherapy. This model directly addresses the clinical problem of choosing between two standard but mechanistically distinct first-line regimens.

This study's limitations include its modest sample size from a single center, which limits the statistical power of some subgroup analyses and precludes the establishment of a definitive PD-1 cutoff value. The use of two different PD-1 inhibitors, though mechanistically similar, may introduce heterogeneity. Future large-scale, multi-center validation studies are essential to standardize the PD-1 assay, confirm the optimal cutoff, and prospectively verify the clinical utility of this combined biomarker model.

Conclusion

In conclusion, while both first-line combination therapies are effective overall, a one-size-fits-all approach is suboptimal. The integration of peripheral blood PD-1 expression on CD4$^+$ or CD8$^+$ T cells together with tumor PD-L1 expression demonstrated a more nuanced and powerful tool for personalizing first-line therapy in advanced NSCLC. This strategy harnesses the convenience of liquid biopsy to reflect both local and systemic immunity, moving us closer to the goal of truly precision medicine in oncology.

Declarations

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Availability of data and material

The corresponding author can provide the datasets used and/or analyzed during the current study upon reasonable request.

Clinical trial number

Not applicable

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Ethics statement

Patient enrollment and treatment were conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Beijing Chest Hospital, Capital Medical University (Approval No.: KY-2018-002). All patients provided written informed consent before treatment initiation.

Author contributions

Wenyun Jia: Conceptualization, Data curation, Writing-original draft; **Xiaomi Li:** Data curation, Formal analysis, Writing-original draft; **Qunhui Wang:** Data curation; **Zhe Qian:** Data curation; **Baolan Li:** Conceptualization, Writing-review & editing; **Tongmei Zhang:** Conceptualization, Writing-review & editing.

Competing interests

All authors declare no conflicts of interest.

Consent for publication

Not applicable

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