Journal of Multidisciplinary Healthcare

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Comparison of the Efficacy of Immune Checkpoint Inhibitors Combined with Chemotherapy Versus Bevacizumab Combined with Chemotherapy in Advanced Driver Gene-Negative Non-Squamous Non-Small Cell Lung Cancer: A Retrospective Study

Wanwan Chen[1], Qiang Dai[2], Zhe Ye[3], Yiwei Huang[3]

[1]Department of Pathology, The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, Wenzhou, Zhejiang, 325000, People's Republic of China; [2]Department of Oncology, the Third Affiliated Hospital of Wenzhou Medical University (Ruian People's Hospital), Wenzhou, Zhejiang, 325200, People's Republic of China; [3]Department of Radiotherapy, the Third Affiliated Hospital of Wenzhou Medical University (Ruian People's Hospital), Wenzhou, Zhejiang, 325200, People's Republic of China

Correspondence: Yiwei Huang, Email ghp503@126.com

Journal of Multidisciplinary Healthcare downloaded from https://www.dovepress.com/
For personal use only.

Objective: To compare the efficacy and safety of immune checkpoint inhibitors (ICIs) plus chemotherapy versus bevacizumab plus chemotherapy in advanced driver gene-negative non-squamous non-small cell lung cancer (NS-NSCLC).

Methods: This retrospective cohort study included 199 patients treated from October 2015 to January 2022. Group A (n=103) received ICIs plus chemotherapy (pemetrexed + cisplatin), while Group B (n=96) received bevacizumab plus the same chemotherapy. Outcomes included treatment response, serum tumor markers (CEA, CA-125, CA-199), immunoglobulins (IgA, IgG, IgM), adverse reactions, and survival [progression-free survival (PFS), overall survival (OS)].

Results: Group A had a significantly higher objective response rate (59.22% vs 36.46%, P=0.001). Tumor marker levels decreased more in Group A (P<0.05), while declines in immunoglobulin levels were less pronounced (P<0.05). Adverse events were similar between groups (P>0.05). Group A had a longer median PFS (11.13 vs 7.37 months, P<0.05), and a non-significant trend toward longer OS (20.87 vs 18.4 months, P=0.159).

Conclusion: ICIs combined with chemotherapy improved treatment efficacy and PFS compared to bevacizumab-based therapy in advanced driver gene-negative NS-NSCLC, with manageable safety and less impact on immune function.

Keywords: immune checkpoint inhibitors, chemotherapy, bevacizumab, non-squamous non-small cell lung cancer, driver gene-negative

Introduction

Advanced driver gene-negative non-squamous non-small cell lung cancer (NS-NSCLC) is the most common type of lung cancer worldwide. Due to its high malignancy and poor prognosis, it remains a major challenge in oncology. Epidemiological data indicate that patients with advanced driver gene-negative NS-NSCLC often experience rapid disease progression and limited treatment options, contributing to persistently low 5-year survival rates.[1,2] Although the expansion of treatment modalities—including chemotherapy, targeted therapies, and immunotherapy—has improved clinical outcomes, the efficacy of conventional regimens is still restricted by tumor heterogeneity, drug resistance, and systemic toxicity.[3,4] For decades, platinum-based chemotherapy, such as pemetrexed combined with cisplatin, has served as a standard first-line treatment for this patient population.[5,6] While this approach can alleviate symptoms and modestly extend survival, its overall therapeutic benefit remains suboptimal, and cumulative toxicities often compromise patients' tolerance.[7]

Received: 21 April 2025
Accepted: 17 July 2025
Published: 29 July 2025

© 2025 Chen et al. This work is published and licensed by Dove Medical Press Limited. The full terms of this license are available at https://www.dovepress.com/terms.php and incorporate the Creative Commons Attribution – Non Commercial (unported, v4.0) License (http://creativecommons.org/licenses/by-nc/4.0/). By accessing the work you hereby accept the Terms. Non-commercial uses of the work are permitted without any further permission from Dove Medical Press Limited, provided the work is properly attributed. For permission for commercial use of this work, please see paragraphs 4.2 and 5 of our Terms (https://www.dovepress.com/terms.php).

The advent of immunotherapy, particularly immune checkpoint inhibitors (ICIs) targeting PD-1/PD-L1, has revolutionized lung cancer treatment. ICIs enhance anti-tumor immune responses by restoring T-cell activity, thereby offering durable responses in subsets of patients with advanced NSCLC.[8,9] Multiple high-quality clinical trials have validated the efficacy of ICIs, showing marked improvements in progression-free survival (PFS) and overall survival (OS).[10] Recent large-scale studies further support the clinical value of ICI-based regimens, especially in patients without actionable mutations.[11–13] Additionally, real-world evidence and meta-analyses continue to refine patient selection and management strategies.[14,15]

Nevertheless, challenges remain. Not all patients benefit equally from immunotherapy due to individual variations in tumor immune microenvironment, PD-L1 expression levels, and immune-related adverse events (irAEs), which may hinder long-term treatment adherence. To overcome these limitations, combined regimens of ICIs with chemotherapy are increasingly adopted, leveraging their complementary mechanisms—cytotoxic killing of tumor cells and immune activation—to achieve synergistic effects.[16,17] On the other hand, anti-angiogenic therapy, particularly bevacizumab, has been incorporated into combination regimens to improve drug delivery and tumor oxygenation. Bevacizumab inhibits VEGF-mediated neovascularization, thereby suppressing tumor growth and progression.[18] Clinical studies have confirmed its efficacy in combination with chemotherapy for advanced NS-NSCLC, offering improvements in both survival and quality of life.[19]

However, direct comparisons between ICIs plus chemotherapy versus bevacizumab plus chemotherapy in the treatment of advanced driver gene-negative NS-NSCLC remain limited. Both strategies have shown promising outcomes, yet their relative efficacy, safety profiles, and long-term benefits remain unclear. Therefore, this retrospective study aims to evaluate and compare the clinical efficacy, safety, and survival outcomes of these two combination regimens, with the goal of informing individualized treatment strategies and optimizing clinical decision-making.

Subjects and Methods

Study Subjects

A retrospective analysis was conducted on the clinical data of 199 patients with advanced driver gene-negative non-squamous non-small cell lung cancer (NS-NSCLC) who received treatment at our hospital between October 2015 and January 2022. Inclusion criteria: (1) Meeting the diagnostic criteria for driver gene-negative NS-NSCLC[20] and confirmed by pathological examination; (2) Age >18 years and <75 years, regardless of gender; (3) TNM staging[21] classified as stage IV; (4) Estimated survival time ≥6 months; (5) Possessing normal comprehension and communication abilities; (6) All participants signed informed consent before the study, being fully aware of the study objectives, methods, and possible risks. Exclusion criteria: (1) Patients with severe comorbidities such as acute heart disease, severe infections, chronic liver disease, or renal failure who are unable to tolerate chemotherapy; (2) Patients with a history of immune system diseases or currently receiving immunosuppressive therapy; (3) Patients diagnosed with active tuberculosis or a history of tuberculosis without effective treatment; (4) Patients with a history or presence of other malignancies; (5) Female patients who are pregnant, breastfeeding, or potentially pregnant; (6) Patients who underwent major surgery within 6 months prior to enrollment; (7) Patients with allergies or contraindications to the drugs or methods used in this study; (8) Patients unable to understand or cooperate with the study protocol due to cognitive impairment, mental illness, or other reasons affecting adherence to treatment requirements. Based on the treatment regimens received, patients were divided into group A (n=103) and group B (n=96). This study was approved by the Ethics Committee of Third Affiliated Hospital of Wenzhou Medical University (Ruian People's Hospital) (Approval No.: YJ2023086) and was conducted in strict accordance with the ethical standards of the Declaration of Helsinki. As this was a retrospective observational study, patients were assigned to treatment groups based on clinical decisions rather than randomization. Although baseline characteristics between the two groups showed no statistically significant differences, some variables—such as gender and age—were close to the threshold of significance, suggesting the possibility of selection bias. Due to the limitations of the study design, multivariate adjustment was not performed, and the potential impact of confounding factors cannot be fully ruled out.

Methods

Before each treatment cycle, patients underwent comprehensive examinations, including complete blood count, liver and kidney function tests, chest CT or PET/CT imaging, to evaluate tumor status. After each chemotherapy session, patients remained in the observation area for 2–4 hours to monitor vital signs, allergic reactions, and post-injection responses, and

to promptly manage any adverse reactions. All patients received a treatment regimen of pemetrexed combined with cisplatin: one cycle every 21 days. On day 1 of each cycle, patients received an intravenous infusion of pemetrexed (Eli Lilly and Company, National Drug Approval No. H20100076) at a dose of 500 mg/m². Prior to infusion, patients took oral folic acid and received vitamin B12 injections before and after treatment to prevent myelosuppression and other toxic side effects. On the same day, cisplatin (Jiangsu Hengrui Pharmaceutical Co., Ltd., National Drug Approval No. H20040813) was administered intravenously at a dose of 75 mg/m² over approximately 6 hours. To reduce cisplatin-induced nephrotoxicity and gastrointestinal reactions, patients were adequately hydrated and pretreated with antiemetic drugs (such as 5-HT3 receptor antagonists combined with dexamethasone). During treatment, renal function, electrolyte levels, and adverse reactions were regularly monitored to allow timely adjustment of the subsequent therapeutic regimen. Group A patients also received ICIs therapy on day 1 of each chemotherapy cycle. The ICI used was pembrolizumab (Registration No. S20180019), administered intravenously at a dose of 200 mg per session, with infusion lasting more than 30 minutes. Group B patients additionally received bevacizumab (Roche Diagnostics GmbH, Approval No.: S20120069) on day 1 of each chemotherapy cycle, administered by intravenous infusion at a dose of 15 mg/kg. All patients underwent evaluation after 2–3 consecutive treatment cycles to assess treatment efficacy.

Observation Indicators

Treatment efficacy

Assessed every 2–3 cycles based on the clinical efficacy criteria for solid tumors.[22] Complete Response (CR): Disappearance of all lesions with no new lesions observed. Partial Response (PR): Decrease in the longest diameter of lesions by >30%. Stable Disease (SD): Decrease in the longest diameter of lesions <30% or increase <20%. Progressive Disease (PD): Increase in the longest diameter of lesions by ≥20%. These responses must persist for more than 4 weeks to be validated. DCR = (CR + PR + SD cases) / total cases × 100%; ORR = (CR + PR cases) / total cases × 100%.

Serum tumor markers

Before and after treatment, 5 mL of fasting elbow venous blood was collected from each patient in the morning. After standard centrifugation, serum supernatant was obtained, and levels of carcinoembryonic antigen (CEA), carbohydrate antigen-125 (CA-125), and carbohydrate antigen-199 (CA-199) were measured using a fully automatic biochemical analyzer.

Immunoglobulin levels

Using the remaining serum samples (detection method as above), the levels of immunoglobulins IgA, IgG, and IgM were measured with a fully automatic biochemical analyzer.

Adverse Reactions

Adverse events during treatment were recorded based on the Common Terminology Criteria for Adverse Events (CTCAE) issued by the US National Cancer Institute (NCI).[23] The evaluated toxicities included nausea and vomiting, abnormal blood pressure, myelosuppression, gastrointestinal reactions, skin reactions, hepatic and renal dysfunction, as well as immune-related adverse events (irAEs).

Survival status

All patients were followed up for 24 months after treatment. Patients were contacted on the 1st day of each month to return to the hospital for imaging review. The endpoint of follow-up was death or loss to follow-up. Progression-Free Survival (PFS): From the start of treatment to disease progression or death. Overall Survival (OS): From the start of treatment to death.

Statistical Analysis

GraphPad Prism 8 was used for plotting and SPSS 22.0 for data processing. Measurement data were expressed as ($\bar{x} \pm s$). Between-group comparisons were conducted using independent sample t-tests, while within-group comparisons employed paired t-tests. Categorical data were expressed as rates (%) and analyzed using the chi-square test for unordered data and the rank-sum test for ordered data. Survival analysis was performed using the Kaplan-Meier method, and differences between groups were compared using the Log rank test. A p-value of <0.05 was considered statistically significant.

Results

Comparison of Baseline Data

There were no significant differences between the two groups in terms of gender, age, ECOG score, smoking history, body mass index (BMI), pathological type, or primary tumor site (P > 0.05), indicating comparability between the groups. See Table 1.

Comparison of Treatment Efficacy

The ORR of Group A was significantly higher than that of Group B (P < 0.05). Although the DCR of Group A was higher than that of Group B, the difference was not statistically significant (P > 0.05). See Table 2.

Comparison of Serum Tumor Marker Levels

Post-treatment levels of CEA, CA-125, and CA-199 in both groups were significantly lower than pre-treatment levels, with Group A showing greater reductions (P < 0.05). See Figure 1.

Table 1 Comparison of Baseline Data [n (%)]

	Group A (n=103)	Group B (n=96)	x^2	P
Gender	–	–	3.724	0.053
Female	15 (14.6%)	26 (27.1%)	–	–
Male	88 (85.4%)	70 (72.9%)	–	–
Age	–	–	3.565	0.059
≤60	23 (22.3%)	33 (34.4%)	–	–
>60	80 (77.7%)	63 (65.6%)	–	–
ECOG Score	–	–	0.681	0.409
≤1	67 (65.0%)	57 (59.4%)	–	–
2	36 (35.0%)	39 (40.6%)	–	–
Smoking History	–	–	0.078	0.780
No	39 (47.6%)	58 (49.6%)	–	–
Yes	43 (52.4%)	59 (50.4%)	–	–
BMI	–	–	0.087	0.958
<18.5	13 (12.6%)	13 (13.5%)	–	–
≥24.0	29 (29.1%)	29 (30.2%)	–	
Pathological Type	–	–	0.221	0.638
Adenocarcinoma	96 (93.2%)	91 (94.8%)	–	–
Others	7 (6.8%)	5 (5.2%)	–	–
Primary Tumor Site	–	–	5.006	0.082
Left Lung	50 (48.5%)	38 (39.6%)	–	–
Right Lung	51 (49.5%)	50 (52.1%)	–	–
Both Lungs	2 (2.0)	8 (8.3%)	–	–

Table 2 Comparison of Treatment Efficacy [n (%)]

TreatmentEfficacy	Group A (n=103)	Group B (n=96)	x^2	P
CR	2 (1.9%)	0 (0.0%)	–	–
PR	59 (57.3%)	35 (36.5%)	–	–
SD	30 (29.1%)	40 (41.7%)	–	–
PD	12 (11.7%)	21 (21.9%)	–	–
ORR	61 (59.2%)	35 (36.5%)	10.313	0.001
DCR	91 (88.4%)	75 (78.1%)	3.755	0.053

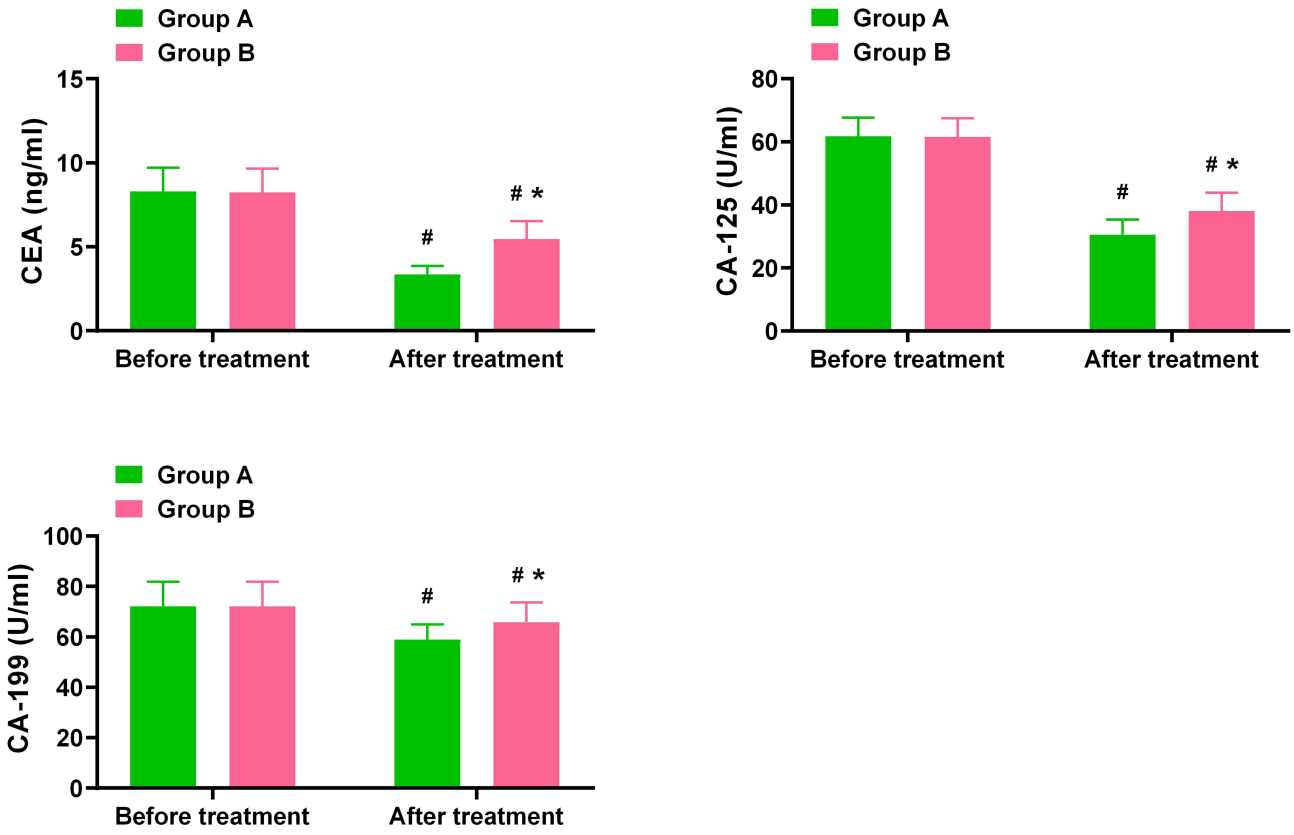

Figure 1 Comparison of Serum Tumor Marker Levels ($\bar{x} \pm s$).
Notes: Between-group comparison, *P < 0.05; comparison with pre-treatment in the same group, #P < 0.05.

Comparison of Immunoglobulin Levels

Post-treatment levels of IgA, IgG, and IgM were reduced in both groups, with smaller reductions observed in Group A ($P < 0.05$). See Figure 2.

Comparison of Toxic Side Effects

Most adverse effects in both groups were grade 1 or 2, with rare occurrences of grade 3 or 4. All adverse reactions resolved after symptomatic treatment. There were no significant differences between the two groups in the incidence of nausea and vomiting, abnormal blood pressure, myelosuppression, gastrointestinal reactions, skin reactions, or liver and kidney dysfunction ($P > 0.05$). See Table 3. In the ICIs group, a total of 27 patients (26.2%) experienced irAEs. These included grade 1–2 rash (9.7%), grade 1–2 thyroid dysfunction (8.7%), grade 1 pneumonitis (3.9%), and grade 2 immune-related hepatitis (3.9%). All irAEs were managed with supportive care or low-dose corticosteroids, and no grade ≥3 irAEs were observed. See Table 4.

Comparison of Survival Outcomes

No loss to follow-up occurred in either group. The median PFS in Group A was 11.13 months (95% confidence interval [CI]: 8.02–14.25), significantly longer than that of Group B at 7.37 months (95% CI: 5.69–9.05; hazard ratio [HR]: 0.67; 95% CI: 0.49–0.91; $P < 0.05$). The median OS in Group A was 20.87 months (95% CI: 18.73–23.01), showing a trend of improvement over Group B at 18.42 months (95% CI: 15.72–21.08; HR: 0.77; 95% CI: 0.53–1.11; $P = 0.159$). See Figures 3 and 4.

Discussion

The results of this study indicate that ICIs combined with chemotherapy demonstrate superior efficacy compared to bevacizumab combined with chemotherapy in patients with advanced driver gene-negative non-squamous non-small cell

https://doi.org/10.2147/JMDH.S535853

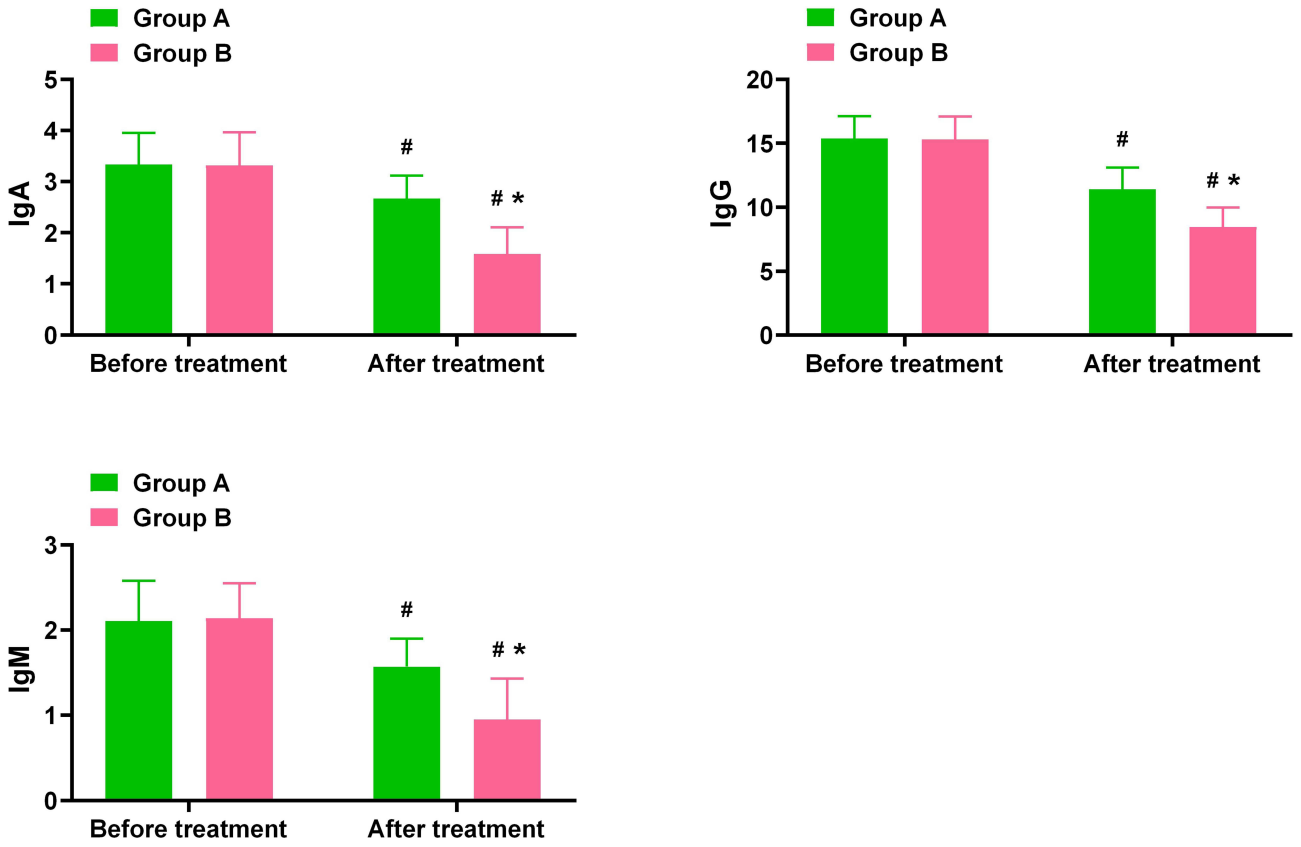

Figure 2 Comparison of Immunoglobulin Levels ($\bar{x} \pm s$, g/L).
Notes: Between-group comparison, *P < 0.05; comparison with pre-treatment in the same group, #P < 0.05.

lung cancer (NSCLC). Specifically, the ORR of the ICIs+chemotherapy group was significantly higher than that of the bevacizumab+chemotherapy group (P<0.05). Although there was no statistically significant difference in disease control rate (DCR) between the two groups, the difference in ORR suggests that the ICIs+chemotherapy regimen may exhibit more prominent effects in enhancing treatment efficacy. The underlying reason lies in the mechanism of ICIs combined with chemotherapy, which primarily activates the immune system and remodels the tumor microenvironment in the treatment of advanced driver gene-negative non-squamous NSCLC. Tumor cells can evade immune surveillance by expressing immune checkpoint molecules (such as PD-L1), which bind to PD-1 receptors on T cells, thereby suppressing their function and activity.[24] ICIs target these immune checkpoint molecules, restore tumor-specific T cell function, enhance immune recognition and attack on tumors, and significantly boost anti-tumor responses.[25] In contrast, bevacizumab primarily inhibits tumor angiogenesis, reducing tumor blood supply and nutrient availability to indirectly limit tumor growth,[26] but does not directly modulate the immune system. Therefore, ICIs combined with chemotherapy not only restrict tumor growth through direct

Table 3 Comparison of Toxic Side Effects [n (%)]

Adverse Reactions	Group A (n=103)	Group B (n=96)	x^2	P
Nausea and Vomiting	47 (45.6%)	51 (53.1%)	1.116	0.290
Abnormal Blood Pressure	28 (27.2%)	21 (21.9%)	0.754	0.385
Myelosuppression	55 (53.4%)	43 (44.8%)	1.472	0.225
Gastrointestinal Reaction	48 (46.6%)	41 (42.7%)	0.304	0.581
Skin Reaction	34 (33.0%)	27 (28.1%)	0.557	0.455
Liver and Kidney Dysfunction	27 (26.2%)	26 (27.1%)	0.019	0.886

Table 4 Incidence and Grade of irAEs in the ICIs Group (n = 103)

Type of irAE	CTCAE Grade	No. of Patients (n)	Incidence Rate (%)
Rash	Grade 1–2	10	9.7%
Thyroid dysfunction	Grade 1–2	9	8.7%
Pneumonitis	Grade 1	4	3.9%
Immune-related hepatitis	Grade 2	4	3.9%
Total (any irAE)	Grade 1–2	27	26.2%
Severe irAEs (Grade ≥3)	–	0	0%

Notes: All immune-related adverse events were managed with supportive care or low-dose corticosteroids. No patients discontinued treatment due to irAEs.

cytotoxic effects but also activate the immune system, with these effects synergizing to enhance efficacy in patients with advanced driver gene-negative non-squamous NSCLC, making it superior to bevacizumab combined with chemotherapy.

Research[27] has indicated that tumor patients generally exhibit significant imbalance in tumor marker levels, with CEA, CA-125, and CA-199 being sensitive markers for evaluating disease severity in cancer patients. CEA, located on tumor cell membranes derived from endodermal differentiation, is upregulated as tumor burden increases and can predict tumor progression to some extent.[28] CA-125 and CA-199 are often used in auxiliary tumor diagnosis, treatment monitoring, and prognosis assessment. Their elevated expression reflects increased tumor burden and heightened cellular metabolic activity.[29,30] In this study, ICIs combined with chemotherapy significantly reduced the levels of tumor markers such as CEA, CA-125, and CA-199, indicating strong tumor-suppressive capability. In contrast, bevacizumab combined with chemotherapy showed a more limited ability to reduce tumor marker levels. The anti-tumor effects of ICIs are closely related to immune system activation; by lifting T cell suppression, ICIs enhance tumor cell recognition and clearance, leading to decreased serum tumor marker levels. Furthermore, other studies[31] have noted that during chemotherapy, drugs may not only kill or slow cancer cell growth but also affect normal cells. IgA, IgM, and IgG are sensitive indicators for evaluating immune function; declines in their levels can reduce antibacterial, immune, and anti-infective capacities, thus affecting overall treatment efficacy.[32,33] The results of this study show that ICIs combined with chemotherapy had minimal impact on immunoglobulin levels (IgA, IgG, IgM), suggesting that ICIs may not only enhance tumor-specific immune responses but also maintain immune homeostasis by preventing systemic immune overactivation. In contrast, bevacizumab indirectly inhibits tumor growth via anti-angiogenesis without directly acting on the immune system, resulting in lesser impact on tumor marker and immunoglobulin levels. This further confirms that immunotherapy offers stronger immune regulatory effects compared to anti-angiogenesis therapy.

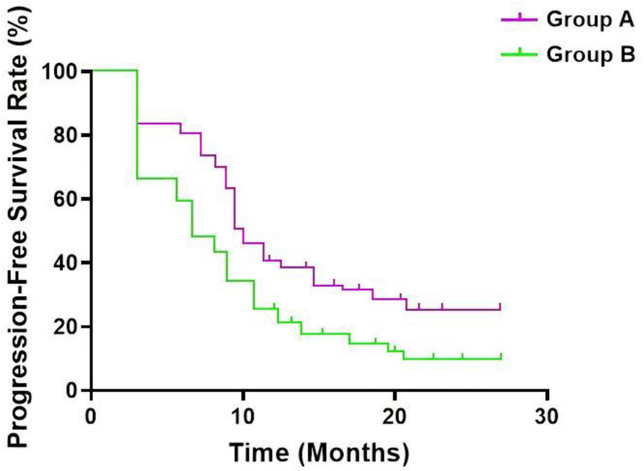

Figure 3 PFS Curves of the Two Groups.

https://doi.org/10.2147/JMDH.S535853

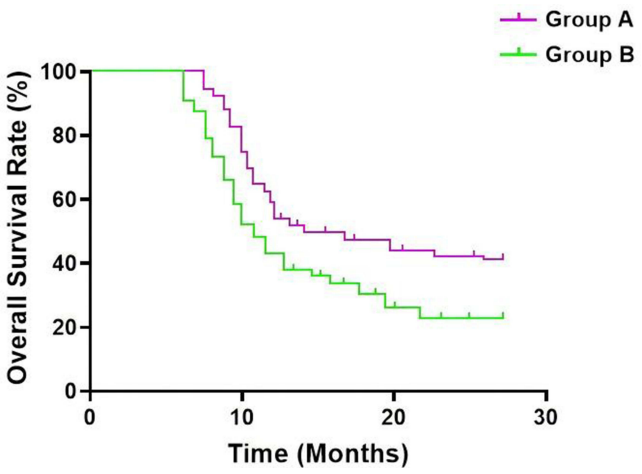

Figure 4 OS Curves of the Two Groups.

Survival time is a key indicator in evaluating cancer treatment efficacy. The results of this study showed that the median PFS in the ICIs+chemotherapy group was significantly longer than in the bevacizumab+chemotherapy group. The reason may be that ICIs restore and enhance immune responses by removing immune suppression, enabling more complete tumor cell clearance, thereby reducing recurrence and metastasis risks, and extending patient survival. One major advantage of immunotherapy over bevacizumab is its durability. While bevacizumab generally provides short-term assistance in tumor cell eradication, immunotherapy can induce durable immune memory through immune system activation,[34,35] maintaining tumor surveillance long after treatment. Notably, while PFS was significantly longer in the ICIs group compared to the bevacizumab group, the difference in OS did not reach statistical significance. This discrepancy may be attributed to several factors. First, the median follow-up duration of this study may have been insufficient to fully capture long-term OS benefits, especially given that many patients were still alive at the end of the study period. Second, potential differences in subsequent-line therapies after disease progression could have influenced OS outcomes. Although detailed data on post-progression treatments were not fully available for all patients, it is possible that patients in the bevacizumab group received ICIs later, which could have partially offset survival differences. Lastly, crossover treatments and differences in patient responses to subsequent regimens may also confound OS results. Future prospective studies with standardized post-treatment protocols and longer follow-up periods are needed to clarify the long-term survival benefits of these regimens.

ICIs-related toxicities are typically associated with immune system activation, leading to a distinct profile of irAEs such as skin reactions and endocrine dysfunctions. In this study, however, there were no statistically significant differences between the ICIs plus chemotherapy group and the bevacizumab plus chemotherapy group in the incidence of common adverse reactions, including nausea and vomiting, abnormal blood pressure, myelosuppression, gastrointestinal reactions, skin reactions, and hepatic or renal dysfunction. Notably, patients in the ICIs group experienced several mild to moderate irAEs, including rash, thyroid dysfunction, pneumonitis, and immune-related hepatitis. These events were mostly grade 1–2 and were effectively managed with supportive care or low-dose corticosteroids. Importantly, no grade ≥3 irAEs or treatment-related discontinuations occurred in the ICIs group. Although immunotherapy may carry a risk of more serious toxicities, the relatively low incidence and manageable nature of irAEs observed in this study suggest that ICIs combined with chemotherapy offer a favorable safety profile. The absence of severe irAEs may be attributed to timely identification and intervention. Therefore, in patients with advanced driver gene-negative non-squamous NSCLC, this combination regimen not only improves clinical efficacy but also maintains acceptable safety, making it a viable and promotable therapeutic strategy.

Despite the strong support this study provides for ICIs combined with chemotherapy, some limitations remain. First, its retrospective and non-randomized design may have introduced selection bias. While baseline variables appeared balanced overall, differences in gender and age approached statistical significance, potentially affecting treatment

outcomes. Additionally, no multivariate analysis was conducted to adjust for confounding variables, which may limit the internal validity of the findings. Second, the single-center setting and relatively small sample size restrict the generalizability of the results. Future multicenter, large-scale prospective studies are warranted to confirm the efficacy and safety of this combination regimen across diverse clinical settings. In addition, the efficacy of immune checkpoint inhibitors may be influenced by patients' genetic background, tumor mutational burden, and PD-L1 expression. Future studies should further explore these factors to support individualized treatment strategies.

Conclusion

This retrospective study demonstrated that ICIs combined with chemotherapy are more effective than bevacizumab combined with chemotherapy in the treatment of advanced driver gene-negative non-squamous NSCLC. The ICIs-based regimen was associated with improved progression-free survival, a trend toward longer overall survival, greater reductions in tumor marker levels, and a milder impact on immune function. Moreover, the safety profiles were comparable between the two regimens, with no increase in severe adverse events observed in the ICIs group. These findings support the use of ICIs plus chemotherapy as a promising and safe first-line treatment strategy in this patient population. However, given the limitations of our single-center, retrospective design, further prospective multicenter studies are needed to validate these results and guide personalized treatment approaches.

Data Sharing Statement

All data generated or analysed during this study are included in this published article.

Ethical Approval Statement

This study was approved by the ethics committee of the Third Affiliated Hospital of Wenzhou Medical University. Informed consent was obtained from all study participants. All the methods were carried out in accordance with the Declaration of Helsinki.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

Project No. Y2023918 of Wenzhou Science and Technology Bureau.

Disclosure

The authors declare that they have no competing interests in this work.

References

1. Chinese expert consensus on antiangiogenic drugs for advanced non-small cell lung cancer (2020 Edition). *Zhonghua Zhong Liu Za Zhi*. 2020;42(12):1063–1077. doi:10.3760/cma.j.cn112152-20200918-00836
2. Zheng H, Zhao D, Gu M, et al. Clinical characteristics and prognostic factors of epidermal growth factor receptor-mutated non-small cell lung cancer transformed into small-cell lung cancer after treatment. *Zhonghua Yi Xue Za Zhi*. 2024;104(40):3751–3756. doi:10.3760/cma.j.cn112137-20240422-00952
3. Ma SX, Ma N, Han J, et al. The efficacy and prognostic factors of immunotherapy in advanced non-small cell lung cancer patients with different driver gene mutations. *Zhonghua Yi Xue Za Zhi*. 2022;102(13):922–929. doi:10.3760/cma.j.cn112137-20211025-02352
4. Chinese expert consensus on evaluation and treatment of advanced non-small cell lung cancer with negative driver genes after first-line immunotherapy resistance (2024 edition). *Zhonghua Yi Xue Za Zhi*. 2024;104(6):411–426. doi:10.3760/cma.j.cn112137-20230927-00589
5. Luan T, Shen PX, Zhang YH, et al. Annual therapeutic advances in advanced non-small cell lung cancer in 2024. *Zhonghua Jie He He Hu Xi Za Zhi*. 2025;48(1):72–77. doi:10.3760/cma.j.cn112147-20241103-00655
6. Ai X, Qiu B, Zhou Y, et al. Comparison and quantification of different concurrent chemotherapy regimens with radiotherapy in locally advanced non-small cell lung cancer: clinical outcomes and theoretical results from an extended LQ and TCP model. *Radiother Oncol*. 2022;167:34–41. doi:10.1016/j.radonc.2021.11.033

7. Choi SH, Jin CC, Do SK, et al. Polymorphisms in Glycolysis-Related Genes Are Associated with Clinical Outcomes of Paclitaxel-Cisplatin Chemotherapy in Non-Small Cell Lung Cancer. *Oncology*. 2020;98(7):468–477. doi:10.1159/000504175
8. Mao Y, Wang A, Sheng S, et al. A Comparative Study of the Efficacy and Safety of Immune Monotherapy versus Immunotheray Combined with Chemotherapy in Elderly Patients Aged 75 Years and Above with Advanced Non-small Cell Lung Cancer. *Zhongguo Fei Ai Za Zhi*. 2024;27(9):665–673. doi:10.3779/j.issn.1009-3419.2024.101.21
9. Wang X, Tu M, Jia H, et al. Evaluation of Efficacy and Prognosis Analysis of Stage III-IV SMARCA4-deficient Non-small Cell Lung Cancer Treated by PD-1 Immune Checkpoint Inhibitors plus Chemotherapy and Chemotherapy. *Zhongguo Fei Ai Za Zhi*. 2023;26(9):659–668. doi:10.3779/j.issn.1009-3419.2023.101.26
10. Li J, Yao X, Qiu L, et al. Research Progress in Immune Checkpoint Inhibitors Combination Therapy Applied to Non-small Cell Lung Cancer after EGFR Mutation-targeted Therapy Resistance. *Zhongguo Fei Ai Za Zhi*. 2023;26(5):392–399. doi:10.3779/j.issn.1009-3419.2023.101.17
11. Sensi B, Angelico R, Toti L, Coppola A, Tisone G. Mechanism, Potential, and Concerns of Immunotherapy for Hepatocellular Carcinoma and Liver Transplantation. *Curr Mol Pharmacol*. 2024;17:e18761429310703. doi:10.2174/0118761429310703240823045808
12. Qiong L, Shuyao X, Qian F, Jiaying T, Yao X, Hui L. Recent Advances in the Glycolytic Processes Linked to Tumor Metastasis. *Curr Mol Pharmacol*. 2024;17:e18761429308361. doi:10.2174/0118761429308361240823061634
13. Manohar SM. At the Crossroads of TNF α Signaling and Cancer. *Curr Mol Pharmacol*. 2024;17(1):e060923220758. doi:10.2174/1874467217666230908111754
14. Gao Z, Jiang A, Li Z, et al. Heterogeneity of Intratumoral Microbiota Within the Tumor Microenvironment and Relationship to Tumor Development. *Med Research*. 2025;1:32–61. doi:10.1002/mdr2.70006
15. Fang Y, Zeng D, Zeng D, Zeng D, Zeng D, Zeng D. Systematic Investigation of Tumor Microenvironment and Antitumor Immunity With IOBR. *Med Research*. 2025;1(1):136–140. doi:10.1002/mdr2.70001
16. Yao S, Shi K, Zhang Y. Advances in Hyperprogressive Disease in Patients with Advanced Non-small Cell Lung Cancer Treated with Immunotherapy. *Zhongguo Fei Ai Za Zhi*. 2021;24(4):271–278. doi:10.3779/j.issn.1009-3419.2021.101.08
17. Li H, Qin N, Yu M, et al. Evaluation of Response to Immune Checkpoint Inhibitor Monotherapy or Combination with Chemotherapy for Patients with Advanced Non-small Cell Lung Cancer and High PD-L1 Expression. *Zhongguo Fei Ai Za Zhi*. 2021;24(3):161–166. doi:10.3779/j.issn.1009-3419.2021.103.02
18. Wang J, Li K. Research progress of anti-angiogenic drugs in the treatment of small cell lung cancer. *Zhonghua Zhong Liu Za Zhi*. 2020;42(8):624–628. doi:10.3760/cma.j.cn112152-20200217-00097
19. Hisakane K, Atsumi K, Seike M, et al. Utility of atezolizumab plus bevacizumab, carboplatin, and paclitaxel combination for the treatment of advanced non-squamous non-small cell lung cancer patients with malignant pleural effusion. *Transl Lung Cancer Res*. 2024;13(9):2106–2115. doi:10.21037/tlcr-24-347
20. Chinese Medical Association guideline for clinical diagnosis and treatment of lung cancer (2024 edition). *Zhonghua Zhong Liu Za Zhi*. 2024;46(9):805–843. doi:10.3760/cma.j.cn112152-20240510-00189
21. Zhang B, Fang WT, Zhong H. Introduction to the 9(th) edition of TNM classification for lung cancer. *Zhonghua Zhong Liu Za Zhi*. 2024;46(3):206–210. doi:10.3760/cma.j.cn112152-20231017-00203
22. Yue J, Hu NL, Wang X, et al. Evaluation of the efficacy and safety of combination of gemcitabine and nedaplatin for patients with HER-2 negative metastatic breast cancer. *Zhonghua Zhong Liu Za Zhi*. 2021;43(8):883–888. doi:10.3760/cma.j.cn112152-20200809-00723
23. Qin Y, Zhao FY, Zhou Y, et al. Programmed cell death-1 inhibitor combined with rituximab in refractory or relapsed diffuse large B-cell lymphoma: a preliminary efficacy and safety analysis. *Zhonghua Zhong Liu Za Zhi*. 2020;42(12):1034–1039. doi:10.3760/cma.j.cn112152-20200506-00410
24. Chen K, Sun B. Incidence and Risk of PD-1/PD-L1 Inhibitor-associated Pneumonia in Advance Cancer Patients: a Meta-analysis. *Zhongguo Fei Ai Za Zhi*. 2020;23(11):927–940. doi:10.3779/j.issn.1009-3419.2020.103.14
25. Li Y, Zhang L, Chen J. Research progress in immune checkpoint inhibitors in the treatment of oncogene-driven advanced non-small cell lung cancer. *Zhong Nan Da Xue Xue Bao Yi Xue Ban*. 2020;45(4):418–425. doi:10.11817/j.issn.1672-7347.2020.190054
26. Parody-Rúa E, Guevara-Cuellar CA. Cost-Effectiveness of the Addition of Bevacizumab to First-Line Chemotherapy With Carboplatin and Paclitaxel in Patients With Non-Small Cell Lung Cancer. *Value Health Reg Issues*. 2020;23:93–98. doi:10.1016/j.vhri.2020.04.005
27. Peng Q, Wu N, Huang Y, et al. Diagnostic values of conventional tumor markers and their combination with chest CT for patients with stageIA lung cancer. *Zhonghua Zhong Liu Za Zhi*. 2023;45(11):934–941. doi:10.3760/cma.j.cn112152-20220208-00082
28. Lin Y, Li H, Huang M, et al. Auxiliary Diagnostic Value of Tumor Markers in the Cerebrospinal Fluid and Blood for Leptomeningeal Metastasis from Non-small Cell Lung Cancer. *Zhongguo Fei Ai Za Zhi*. 2020;23(6):516–525. doi:10.3779/j.issn.1009-3419.2020.103.09
29. Strum S, Vincent M, Gipson M, et al. Assessment of serum tumor markers CEA, CA-125, and CA19-9 as adjuncts in non-small cell lung cancer management. *Oncotarget*. 2024;15(1):381–388. doi:10.18632/oncotarget.28566
30. Yang X, Xiao Y, Zhou Y, et al. Dynamic monitoring of serum tumor markers as prognostic factors in patients with advanced non-small-cell lung cancer treated with first-line immunotherapy: a multicenter retrospective study. *Ther Adv Med Oncol*. 2023;15:17588359231206282. doi:10.1177/17588359231206282
31. Jin W, Feng L, Hu XS, et al. Efficacy and safety of epidermal growth factor receptor tyrosine kinase inhibitors combined with chemotherapy as first-line treatment for epidermal growth factor receptor-mutant advanced non-small cell lung cancer. *Zhonghua Yi Xue Za Zhi*. 2023;103(16):1196–1201. doi:10.3760/cma.j.cn112137-20221110-02364
32. Wang J, Zhang Y, Gao Y. Relationship between immune indexes and prognosis in patients with sepsis: data analysis based on MIMIC-IV database. *Zhonghua Wei Zhong Bing Ji Jiu Yi Xue*. 2022;34(9):931–934. doi:10.3760/cma.j.cn121430-20211102-01622
33. Zhang M, Ma XL, Duan YL, et al. Analysis of serum immunoglobulin level in children with Burkitt lymphoma. *Zhonghua Er Ke Za Zhi*. 2022;60(4):329–333. doi:10.3760/cma.j.cn112140-20210817-00679
34. Kadam P, Sharma S. PD-1 Immune Checkpoint Blockade Promotes Therapeutic Cancer Vaccine to Eradicate Lung Cancer. *Vaccines*. 2020;8(2):1.
35. Mathew D, Marmarelis ME, Foley C, et al. Combined JAK inhibition and PD-1 immunotherapy for non-small cell lung cancer patients. *Science*. 2024;384(6702):eadf1329. doi:10.1126/science.adf1329

Journal of Multidisciplinary Healthcare

Dovepress
Taylor & Francis Group

Publish your work in this journal

The Journal of Multidisciplinary Healthcare is an international, peer-reviewed open-access journal that aims to represent and publish research in healthcare areas delivered by practitioners of different disciplines. This includes studies and reviews conducted by multidisciplinary teams as well as research which evaluates the results or conduct of such teams or healthcare processes in general. The journal covers a very wide range of areas and welcomes submissions from practitioners at all levels, from all over the world. The manuscript management system is completely online and includes a very quick and fair peer-review system. Visit http://www.dovepress.com/testimonials.php to read real quotes from published authors.

Submit your manuscript here: https://www.dovepress.com/journal-of-multidisciplinary-healthcare-journal