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# Albumin bound-paclitaxel combined with anlotinib and immunotherapy in the second-line treatment of ES-SCLC: a retrospective cohort study

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Effective treatment strategies for second-line therapy in extensive-stage small cell lung cancer (ES-SCLC) are currently lacking. For this reason, we collected and recorded efficacy and safety data from patients with ES-SCLC who had disease progression after first-line treatment and received albumin-bound paclitaxel, anlotinib, and immunotherapy. Preliminary data showed an objective response rate of 37.78%. Median progression-free survival and overall survival were 5 months and 10 months, respectively. Treatment-related adverse events were mostly tolerable. Subgroup analysis indicated that efficacy correlated with the interval from last chemotherapy to treatment initiation and specific drug-related adverse events. Further analysis of immune cell subtypes suggested that the mechanism may involve depletion of immune suppression to activate immune responses synergistically against tumors. With its promising efficacy and manageable adverse effects, this regimen holds potential as a significant option for second-line therapy in ES-SCLC. However, due to the limited sample size, further clinical validation is needed to ascertain its true clinical value.

*Key words: albumin-bound paclitaxel; anlotinib; immunotherapy; ES-SCLC*

Small cell lung cancer (SCLC) is a highly malignant subtype of lung cancer, characterized by rapid growth, strong invasiveness, sensitivity to chemotherapy, but prone to recurrence and drug resistance. Particularly, extensive-stage small cell lung cancer (ES-SCLC) still has a very poor prognosis, with high recurrence rates after first-line treatment, posing a significant clinical challenge [1]. Currently, the combination of etoposide plus cisplatin/carboplatin (EP) and immunotherapy has become the standard first-line treatment for extensive-stage small cell lung cancer [2–5]. However, the efficacy of these treatment regimens is limited, with patients often experiencing disease progression or recurrence in a short period, thus, finding effective second-line treatment strategies is urgently needed [6].

With the in-depth study of tumor immunotherapy, the combination therapy approach is beginning to play an important role in the second-line treatment of ES-SCLC. Although theoretically there are various combinations available [7–10], specific regimens evidently require further optimization. Albumin-bound paclitaxel, as a microtubule inhibitor, has shown certain anti-tumor activity in the treatment of various cancers [11], and its protein-bound properties can improve drug stability and targeting, thus reducing toxic side effects [12, 13]. Anlotinib is a multi-targeted tyrosine kinase inhibitor that has been proven to have inhibitory effects on lung cancer and may enhance the efficacy of immunotherapy through multiple pathways [14, 15]. Therefore, this study aims to explore the safety and efficacy of combination therapy with albumin-bound paclitaxel, anlotinib, and immunotherapy in the second-line treatment of ES-SCLC with the objective of providing new ideas and methods for the treatment of SCLC.

## Patients and methods

**Patient selection.** This study employed a single-center, retrospective clinical research design. Inclusion criteria comprised: 1) age 18 years or older; 2) diagnosed with ES-SCLC; 3) good general condition and organ function; 4) received first-line chemotherapy and required second-line treatment upon disease progression; 5) acceptable life expectancy and treatment plan; 6) signed informed consent.

Exclusion criteria included: 1) severe cardiovascular disease or autoimmune diseases; 2) severe bleeding tendencies or current use of anticoagulant therapy; 3) active other malignancies; 4) severe hepatic or renal dysfunction; 5) pregnancy or lactation.

**Ethics approval.** The authors assume full responsibility for ensuring the accuracy and integrity of all aspects of the study. Any concerns regarding the precision or honesty of any part of the work were thoroughly investigated and addressed. The study adhered to the principles outlined in the Declaration of Helsinki (revised in 2013). Approval for this retrospective trial was obtained from the Ethics Committee of Hubei Cancer Hospital Affiliated with Tongji Medical College (Wuhan, China) (Approval No. HBCHEC2021168). All participants were included in the study after signing informed consent forms.

**Treatment regimen.** After disease progression (PD), all enrolled patients received nanoparticle albumin-bound paclitaxel (nab-paclitaxel) in combination with anlotinib and immunotherapy as the second-line treatment regimen. The specific treatment regimen was as follows: nab-paclitaxel administered intravenously every three weeks at a dose of 200 mg/m$^2$, anlotinib administered orally at a dose of 12 mg (once a day, for two weeks, followed by a one-week break) and immunotherapy utilizing a PD-1 inhibitor at a dose administered every 3 weeks according to prescription instructions.

**Efficacy assessment.** Efficacy assessment included clinical performance evaluation, imaging assessment, and survival evaluation. Clinical performance evaluation was based on changes in patient symptoms and signs, imaging assessment primarily utilized CT scans, and survival evaluation was conducted using the Kaplan-Meier method. Safety assessment included monitoring adverse events and laboratory testing. Adverse event monitoring was graded according to the Common Terminology Criteria for Adverse Events (CTCAE), and laboratory testing included hematological parameters, liver and kidney function indicators, among others.

**Data analysis.** All data were analyzed using SPSS statistical software. Continuous variables were described as mean ± standard deviation or median (range), while categorical variables were described as frequency and percentage. Survival data were analyzed using the Kaplan-Meier method for survival curve analysis, with the log-rank test employed to compare differences between survival curves.

**Table 1. Baseline clinical characteristics of the study cohort.**

| Characteristics | No. of patients [n (%)] |
|---|---|
| Age | |
| years | 68 |
| range | 47–75 |
| Gender | |
| male | 36 (80.00) |
| female | 9 (20.00) |
| Smoking history | |
| never smoker | 11 (24.44) |
| former smoker | 34 (75.56) |
| ECOG score | |
| 0–1 | 37 (82.22) |
| ≥2 | 8 (17.78) |
| Previous radiotherapy | |
| yes | 14 (31.11) |
| no | 31 (68.89) |
| Previous systemic treatment | |
| etoposide plus cisplatin | 33 (73.33) |
| etoposide plus carboplatin | 12 (26.67) |
| Median chemotherapy-free interval | |
| <90 days | 19 (42.22) |
| ≥90 days | 26 (57.78) |
| Brain metastasis | |
| yes | 8 (17.78) |
| no | 37 (82.22) |
| Liver metastasis | |
| yes | 6 (13.33) |
| no | 39 (86.67) |
| Stage | |
| limited | 9 (20.00) |
| extensive | 36 (80.00) |

## Results

**Patient characteristics.** A total of 45 patients were included in the study, comprising 36 males and 9 females, with a median age of 68 years. The overall performance status of the patients ranged from 0 to 2, with 8 cases exhibiting brain metastasis and 6 cases presenting liver metastasis. The majority of patients had a performance status (PS) of 0–1, while a subset had a PS of 2 (17.78%). Most female patients were non-smokers, whereas the majority of male patients had a history of smoking. The majority of patients were diagnosed with ES-SCLC, with a smaller proportion classified as limited-stage SCLC (20.00%). Regarding sensitivity to prior chemotherapy, 42.22% of patients received no chemotherapy break within 90 days, while 57.78% had a break of 90 days or more after first-line chemotherapy. All participants had undergone at least one line of chemotherapy treatment. The primary regimen for first-line treatment was the EP regimen, the proportions of patients receiving etoposide combined with cisplatin and etoposide combined with carboplatin were 73.33% and 26.67%, respectively. Fourteen patients had also received radiotherapy, with the mean treatment interval before enrollment being approximately 3.5 months. (Table 1).

**Efficiency.** After a median follow-up of 28 months, all 45 participants received the triple combination therapy of PD-1/L1 inhibitors, nab-paclitaxel, and anlotinib. Preliminary results indicated that the overall response rate (ORR) of this regimen in second-line treatment of SCLC patients was 37.78%, with no complete responses (CR), 17 partial

responses (PR), 15 cases of stable disease (SD), and 13 cases of progressive disease (PD); the disease control rate (DCR) was 71.11% (Table 2). The median progression-free survival (mPFS) was 5.0 months, while the median overall survival (mOS) was 10.0 months (Figures 1A, 1B). In subgroup analysis, compared to patients who received no chemotherapy interval within 90 days, those with a chemotherapy-free interval of 90 days or more after first-line chemotherapy exhibited higher efficacy (mPFS 5.0 vs. 4.0 months, HR=3.958, 95% CI: 1.552–10.10, p=0.002; mOS 10.0 vs. 8.0 months, HR=5.437, 95% CI: 2.253–13.12, p=0.002) (Figures 2A, 2B). Additionally, compared to the patients without sAE during the whole treatment, the patients with sAEs achieved better therapeutic effect (mPFS 5.5vs. 4.4 months, HR=9.899, 95% CI: 3.965–24.71, p<0.0001; mOS 10.0 vs. 8.0 months, HR=5.911, 95% CI: 2.638–13.24, p<0.0001 (Figures 2C, 2D), indicating that TFI since the commence of treatment and the occurrence of sAE can be utilized to predict the efficacy of this regimen in ES-SCLC.

**Mechanism exploration.** Since the efficacy may be correlated with immune regulation, we also compared the immune cell reserve before and after treatment in the peripheral blood. Preliminary results indicated that the proportion of Treg cells in patients significantly decreased after treatment. Patients with a decreased proportion of Treg cells exhibited higher ORR as well as DCR (Figure 3). Further analysis showed that patients with Treg depletion after treatment exhibited better efficacy compared to those without Treg depletion (mPFS 5.0 vs. 4.0 months, HR=6.118, 95% CI: 2.474–15.13, p<0.0001; mOS 10.0 vs. 8.5 months, HR=4.357, 95% CI: 1.973–9.621, p=0.0003 (Figures 2E, 2F), indicating that the mechanisms of this regimen may involve depleting immune suppression to further activate the immune system, thus exerting a synergistic anti-tumor effect.

**Safety.** Regarding safety, the adverse effects of the combination therapy were manageable and within acceptable limits. The most commonly observed adverse events comprised hematologic toxicities (such as leukopenia and thrombocytopenia), gastrointestinal reactions (such as decreased appetite, nausea, and vomiting), hypertension, hand-foot syndrome, proteinuria, rash, hyperthyroidism, hypothyroidism, among others. However, the majority of adverse events were mild to moderate in severity and could be effectively managed with appropriate supportive care (Table 3).

## Discussion

ES-SCLC is a highly aggressive lung tumor, and its treatment has always been a clinical challenge. Traditional treatment approaches often have limited efficacy, making it crucial

**Table 2. Clinical activity of anlotinib, nab-ptx, and PD-1/L1 inhibitors in ES-SCLC.**

| | All patients (n = 45) | Chemotherapy-free interval <90 days (n=19) | Chemotherapy-free interval ≥90 days (n=19) |
|---|---|---|---|
| Complete response | 0 | 0 | 0 |
| Partial response | 37.78% (17/45) | 31.58% (6/19) | 42.31% (11/26) |
| Stable response | 33.33% (15/45) | 31.58% (6/19) | 30.77% (8/26) |
| Progressive disease | 28.89% (13/45) | 36.84% (7/19) | 26.92% (7/26) |
| Objective response | 37.78% | 31.58% | 42.31% |
| Median PFS (months) | 5.0 | 4.0 | 5.0 |
| Disease control rate | 71.11% | 63.16% | 73.08% |
| Median OS (months) | 10.0 | 8.0 | 10.0 |

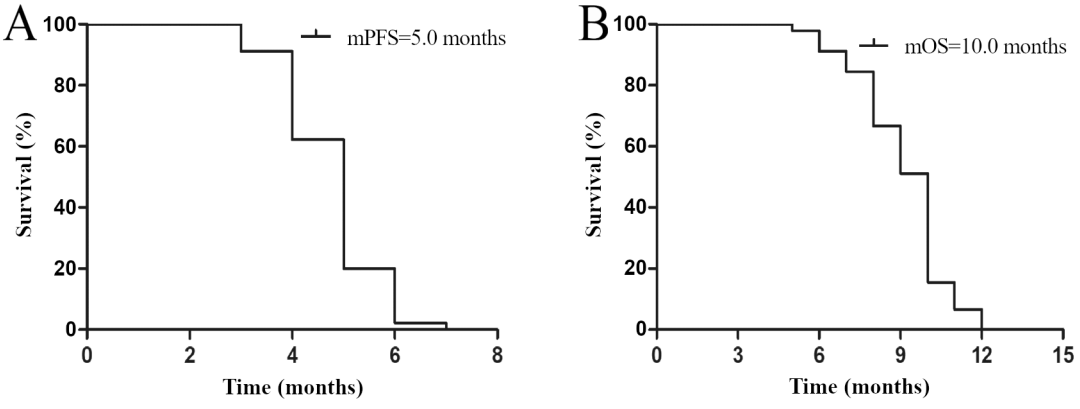


**Figure 1. PFS and OS analysis of general patients with pretreated ES-SCLC who accepted the triple-drug combination of anlotinib, nab-paclitaxel, and PD-1/L1 inhibitors in this study. A and B represent the overall PFS and OS in this study, respectively.**

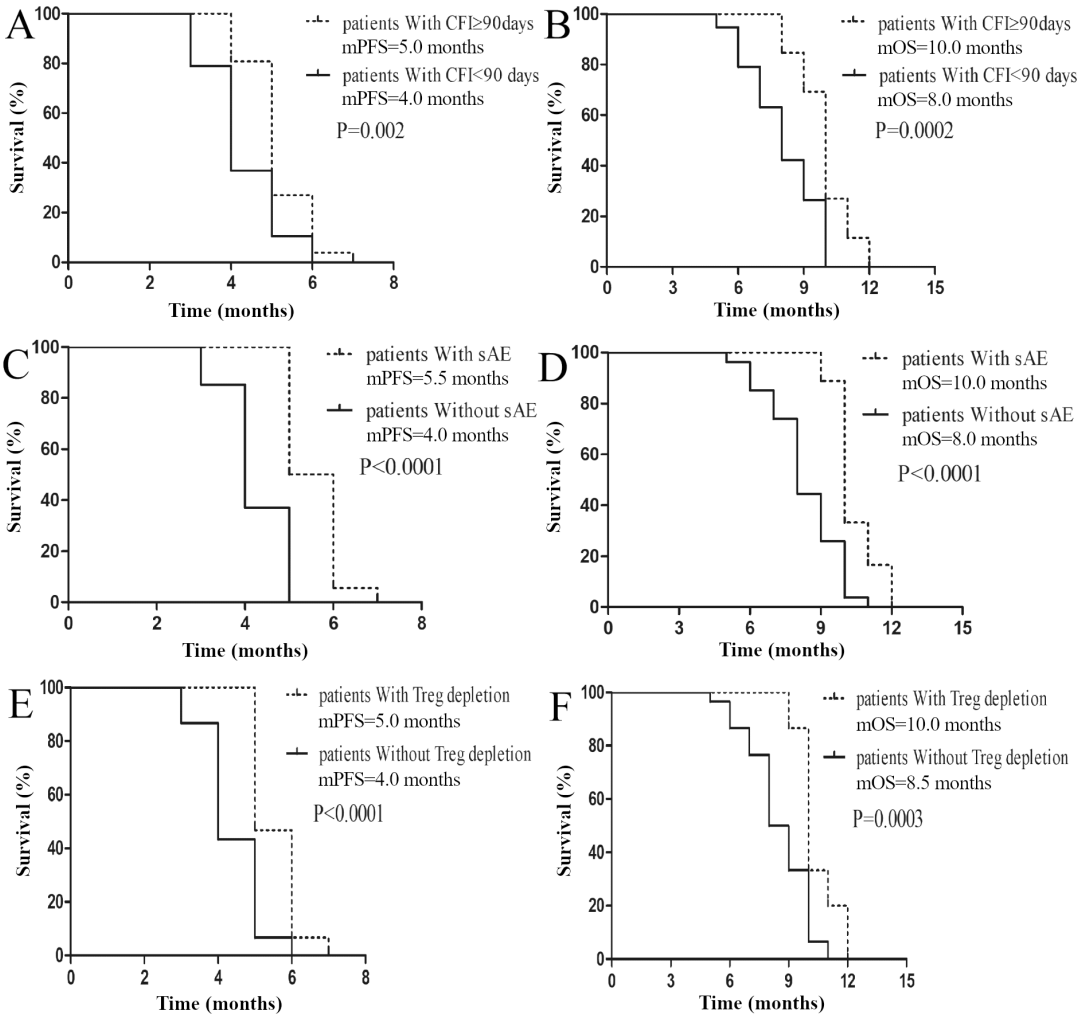


**Figure 2. PFS and OS comparison analysis of the subgroup patients with pretreated ES-SCLC who accepted the triple-drug combination of anlotinib, nab-paclitaxel, and PD-1/L1 inhibitors in this study. A, B) Comparisons of PFS and OS between these patients with CFI<90 days and those patients with CFI≥90 days. C, D) Comparisons of PFS and OS between these patents with sAEs and without during the whole treatment (with sAEs vs. without sAEs). E, F) Comparisons of PFS and OS between these patents with Treg ratio decrease and Treg ratio unchanged (with Treg depletion vs without Treg depletion). Abbreviations: mPFS-median progression-free survival; mOS-median overall survival; SCLC-small cell lung cancer; CFI-chemotherapy-free interval; IO-immuno-oncology; sAE-specifically refers to any adverse event including hypertension, proteinuria, and hand-foot syndrome**

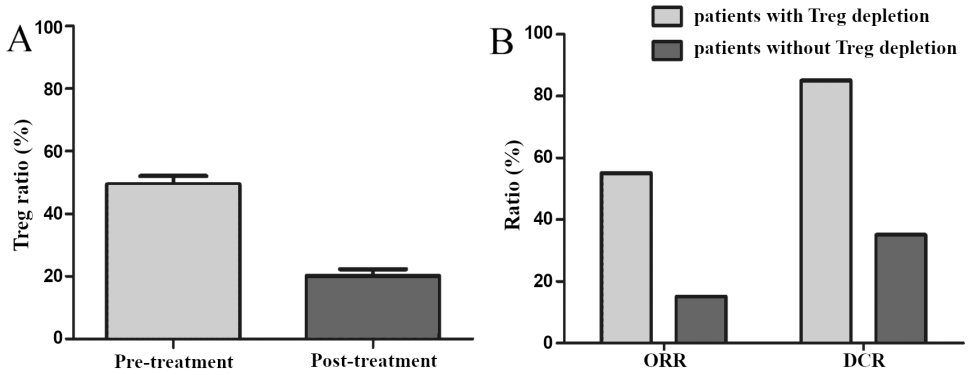


**Figure 3. Changes in the proportion of Treg cells in the peripheral blood of patients with ES-SCLC before and after receiving second-line three-drug combination therapy, as well as a comparison of efficacy among different Treg change populations. Panel A shows the changes in the proportion of Treg cells in peripheral blood before and after treatment (p<0.01); Panel B compares the efficacy between patients with Treg depletion and those without Treg depletion.**

to search for more effective therapeutic strategies [1, 16]. This study aimed to evaluate the efficacy and safety of nab-paclitaxel combined with anlotinib and immunotherapy in the second-line treatment of ES-SCLC and provide valuable insights for clinical practice.

Our study results showed that the combination of nab-paclitaxel with anlotinib and immunotherapy as a new strategy for the second-line treatment of ES-SCLC demonstrated significant clinical benefits. Firstly, we observed that compared to dual-agent combinations (such as immune therapy combined with anti-tumor angiogenesis, chemotherapy combined with immunotherapy, etc.), the triple therapy regimen results in a superior overall survival (OS) [17–19]. In the second-line and beyond the treatment of ES-SCLC, the combination of nab-paclitaxel with anlotinib and immunotherapy can even achieve an OS of up to 10 months. Additionally, the one-year survival rate reached 45% in the triple therapy group, significantly higher than the 30% in the previous study [10, 20, 21]. Secondly, the DCR in the triple therapy group significantly improved. At the evaluation after 8 weeks of treatment, the DCR reached 70% in the triple therapy group compared to only 45% in previous reports [22–24]. This indicates that triple therapy can more effectively control disease progression and slow down disease worsening. Furthermore, there was an improvement in the quality of life in the triple therapy regimen. Patients reported fewer side effects such as pain, nausea, and vomiting after receiving triple therapy while feeling more energy and vitality. This suggests that triple therapy not only prolongs patient survival but also improves their quality of life and alleviates the impact of symptoms [7, 25].

In terms of safety, the combination therapy regimen was manageable and acceptable. The most common adverse events included hematologic toxicity (such as leukopenia, thrombocytopenia) and gastrointestinal reactions (such as nausea, vomiting, diarrhea) [13, 17, 26, 27], most of which were mild to moderate and could be managed with appropriate supportive care. Therefore, the combination therapy regimen meets the safety requirements of clinical practice and does not impose excessive discomfort and risk on patients [28]. Although the study employed a triple therapy combination, there was no apparent increase in adverse reactions. One possible explanation for this phenomenon is that, unlike previous studies, this research utilized a low-dose nab-paclitaxel [29]. Not only can this low-dose chemotherapy induce immunogenic cell death to activate the immune system and enhance the synergistic effect of the regimen [30, 31] but it can also further reduce the toxicity and adverse reactions associated with chemotherapy. This may also be another novel aspect of this study. Interestingly, we also found that the efficacy significantly correlates with the occurrence of sAE and the treatment commence of TFI, indicating that such characteristics can be applied to screen the advantageous population of such regimen. Additionally, by detecting the immune cell composition in the peripheral blood, we also found that compared to patients without Treg depletion before and after the treatment, these patients with Treg depletion show better efficiency, implying that the mechanism of such regimen may be probably lying in depleting immune suppression (Treg, MDSC, et al.) to further activate the immune to exert a synergistic anticancer effect, all of which provide important evidence and direction for the treatment of ES-SCLC in the future. However, regarding the precise synergistic mechanism of the triple therapy, which patients can benefit more from this regimen, and the mechanisms of resistance, further research is evidently required. These are also the focus of our current research efforts.

Our study has the following significance: it is the first to confirm the efficacy of a three-drug combination (nab-pacli-

**Table 3. Adverse events of anlotinib, nab-ptx, and PD-1/L1 inhibitors in ES-SCLC.**

| Adverse event | anlotinib, nab-ptx, and PD-1/L1 [n (%)] | |
|---|---|---|
| | Any grade | Grade 3 or 4 |
| Hematological | | |
| Leukopenia | 15 (33.33) | 3 (6.67) |
| Neutropenia | 14 (31.11) | 3 (6.67) |
| Thrombocytopenia | 12 (26.67) | 2 (4.44) |
| Anemia | 9 (20.00) | 1 (2.22) |
| Nonhematological | | |
| Decreased appetite | 24 (53.33) | 0 |
| Nausea | 20 (44.44) | 0 |
| Vomit | 18 (40.00) | 0 |
| Fatigue | 17 (37.78) | 0 |
| Hypertension | 14 (31.11) | 4 (8.89) |
| Hand-foot syndrome | 15 (33.33) | 4 (8.89) |
| Proteinuria | 12 (26.67) | 4 (8.89) |
| Elevated transaminase | 10 (22.22) | 4 (8.89) |
| Oral ulcer | 9 (20.00) | 0 |
| Stomatitis | 10 (22.22) | 0 |
| Abdominal pain | 8 (17.78) | 0 |
| Diarrhea | 8 (17.78) | 0 |
| Hyperbilirubinemia | 6 (13.33) | 0 |
| Elevated LDH | 8 (17.78) | 0 |
| ALP increased | 7 (15.56) | 0 |
| Elevated GGT | 5 (11.11) | 0 |
| Hypoproteinemia | 6 (13.33) | 0 |
| Dysphagia | 5 (11.11) | 0 |
| Dysphonia | 6 (13.33) | 0 |
| Bleeding | 0 | 0 |
| Immunological | | |
| Hypothyroidism | 16 (35.56) | 0 |
| Hyperthyroidism | 15 (33.33) | 0 |
| Rash | 13 (28.89) | 4 (8.89) |
| Hepatitis | 8 (17.78) | 3 (6.67) |
| Itching | 9 (20.00) | 3 (6.68) |
| Pneumonia | 5 (11.11) | 3 (6.67) |
| Infusion reaction | 4 (8.89) | 1 (2.22) |
| Nephritis | 3 (6.66) | 1 (2.22) |

taxel + anlotinib + PD-1) in the second-line treatment of ES-SCLC, demonstrating better efficacy than previously reported studies [32, 33]. In addition to the general population, the study also included patients with liver and brain metastases, indicating a broad clinical application prospect for this regimen, even in the face of challenges from new drugs for SCLC, such as antibody-drug conjugate [34] and bispecific antibodies [35]. Moreover, after optimization, although this is a multi-drug combination, there was no significant increase in toxicity or side effects, suggesting good tolerability of the regimen, which can further ensure that patients maintain a high quality of life during treatment [36]. Furthermore, our study identified several potential indicators for efficacy prediction, such as the interval without chemotherapy prior to enrollment and the side effects during treatment, providing a basis for selecting optimal patient populations for clinical application. Finally, the study also found that the mechanism of action of this regimen may be related to the downregulation of immune suppression [37], all these findings will contribute to the advancement of treatment for SCLC [38].

In summary, nab-paclitaxel combined with anlotinib and immunotherapy as a new strategy for the second-line treatment of ES-SCLC demonstrates significant efficacy and good safety. This combination therapy regimen is expected to become an important treatment option for ES-SCLC patients and provides valuable insights for future clinical practice. However, we also recognize some limitations of this study [39], such as relatively small sample size and single-center study design, thus further large-scale, multicenter clinical studies are needed to validate our results [40].

In conclusion, with promising efficacy and lower cytotoxicity, nab-paclitaxel combined with anlotinib and immunotherapy holds promise as an important option for second-line treatment in ES-SCLC. However, due to some limitations in this study, such as a relatively small sample size and single-center design, further large-scale, multicenter clinical studies are needed to confirm our findings.

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## References

[1] ZUGAZAGOITIA J, PAZ-ARES L. Extensive-Stage Small-Cell Lung Cancer: First-Line and Second-Line Treatment Options. J Clin Oncol 2022; 40: 671–680. https://doi.org/10.1200/jco.21.01881

[2] HORN L, MANSFIELD AS, SZCZĘSNA A, HAVEL L, KRZAKOWSKI M et al. First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer. N Engl J Med 2018; 379: 2220–2229. https://doi.org/10.1056/NEJMoa1809064

[3] CHENG Y, HAN L, WU L, CHEN J, SUN H et al. Effect of First-Line Serplulimab vs Placebo Added to Chemotherapy on Survival in Patients With Extensive-Stage Small Cell Lung Cancer. JAMA 2022; 328: 1223–1232. https://doi.org/10.1001/jama.2022.16464

[4] PAZ-ARES L, DVORKIN M, CHEN Y, REINMUTH N, HOTTA K et al. Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. Lancet 2019; 394: 1929–1939. https://doi.org/10.1016/S0140-6736(19)32222-6

[5] WANG J, ZHOU C, YAO W, WANG Q, MIN X et al. Adebrelimab or placebo plus carboplatin and etoposide as first-line treatment for extensive-stage small-cell lung cancer (CAPSTONE-1): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2022; 23: 739–747. https://doi.org/10.1016/S1470-2045(22)00224-8

[6] REMON J, ALDEA M, BESSE B, PLANCHARD D, RECK M et al. Small cell lung cancer: a slightly less orphan disease after immunotherapy. Ann Oncol 2021; 32: 698–709. https://doi.org/10.1016/j.annonc.2021.02.025

[7] SMITH KER, MANSFIELD AS. Validating chemoimmunotherapy in small-cell lung cancer. Lancet Oncol 2022; 23: 692–693. https://doi.org/10.1016/s1470-2045(22)00288-1

[8] SPIGEL DR, WATERHOUSE DM, LANE S, LEGENNE P, BHATT K. Efficacy and safety of oral topotecan and bevacizumab combination as second-line treatment for relapsed small-cell lung cancer: an open-label multicenter single-arm phase II study. Clin Lung Cancer 2013; 14: 356–363. https://doi.org/10.1016/j.cllc.2012.12.003

[9] LI D, HUANG Z, ZHONG J, LIN L, ZHANG G et al. Efficacy and safety of fluzoparib combined with anlotinib in extensive stage small cell lung cancer after first-line platinum-based chemotherapy: a multi-center, single-arm prospective phase II clinical study (STAMP study). BMC Cancer 2023; 23: 753. https://doi.org/10.1186/s12885-023-11230-5

[10] YU L, XU J, QIAO R, HAN B, ZHONG H et al. Efficacy and safety of anlotinib combined with PD-1/PD-L1 inhibitors as second-line and subsequent therapy in advanced small-cell lung cancer. Cancer Med 2023; 12: 5372–5383. https://doi.org/10.1002/cam4.5360

[11] CECCO S, ALIBERTI M, BALDO P, GIACOMIN E, LEONE R. Safety and efficacy evaluation of albumin-bound paclitaxel. Expert Opin Drug Saf 2014; 13: 511–520. https://doi.org/10.1517/14740338.2014.893293

[12] OI H, MATSUDA T, KIMURA T, MORISE M, YAMANO Y et al. Weekly nanoparticle albumin-bound paclitaxel and paclitaxel for relapsed small cell lung cancer: A retrospective observational study. Medicine (Baltimore) 2022; 101: e28863. https://doi.org/10.1097/MD.0000000000028863

[13] NAKAO M, FUJITA K, SUZUKI Y, ARAKAWA S, SAKAI Y et al. Nab-paclitaxel Monotherapy for Relapsed Small Cell Lung Cancer: Retrospective Analysis and Review. Anticancer Res 2020; 40: 1579–1585. https://doi.org/10.21873/anticanres.14105

[14] YUAN J, CHENG F, XIAO G, WANG X, FAN H. Efficacy and Safety of Anlotinib in the Treatment of Small Cell Lung Cancer: A Real-World Observation Study. Front Oncol 2022; 12: 917089. https://doi.org/10.3389/fonc.2022.917089

[15] ZHENG HR, JIANG AM, GAO H, LIU N, ZHENG XQ et al. The Efficacy and Safety of Anlotinib in Extensive-Stage Small Cell Lung Cancer: A Multicenter Real-World Study. Cancer Manag Res 2022; 14: 2273–2287. https://doi.org/10.2147/CMAR.S364125

[16] MEIJER JJ, LEONETTI A, AIRÒ G, TISEO M, ROLFO C et al. Small cell lung cancer: Novel treatments beyond immunotherapy. Semin Cancer Biol 2022; 86: 376–385. https://doi.org/10.1016/j.semcancer.2022.05.004

[17] READY NE, OTT PA, HELLMANN MD, ZUGAZAGOITIA J, HANN CL et al. Nivolumab Monotherapy and Nivolumab Plus Ipilimumab in Recurrent Small Cell Lung Cancer: Results From the CheckMate 032 Randomized Cohort. J Thorac Oncol 2020; 15: 426–435. https://doi.org/10.1016/j.jtho.2019.10.004

[18] JIANG HT, LI W, ZHANG B, GONG Q, QIE HL. Efficacy and Safety of Anlotinib Monotherapy as Third-Line Therapy for Elderly Patients with Non-Small Cell Lung Cancer: A Real-World Exploratory Study. Int J Gen Med 2021; 14: 7625–7637. https://doi.org/10.2147/IJGM.S334436

[19] YOSHIDA H, KIM YH, OZASA H, NAGAI H, SAKAMORI Y et al. Albumin-bound paclitaxel for the treatment of refractory or relapsed small-cell lung cancer. Mol Clin Oncol 2016; 5: 213–215. https://doi.org/10.3892/mco.2016.887

[20] IKEDA N, ARAI R, SODA S, INOUE T, UCHIDA N et al. Carboplatin plus nab-paclitaxel for recurrent small cell lung cancer: A phase II study. Thorac Cancer 2022; 13: 1342–1348. https://doi.org/10.1111/1759-7714.14394

[21] KIM YJ, KEAM B, OCK CY, SONG S KIM M et al. A phase II study of pembrolizumab and paclitaxel in patients with relapsed or refractory small-cell lung cancer. Lung Cancer 2019; 136: 122–128. https://doi.org/10.1016/j.lungcan.2019.08.031

[22] VON PAWEL J, SCHILLER JH, SHEPHERD FA, FIELDS SZ, KLEISBAUER JP et al. Topotecan versus cyclophosphamide, doxorubicin, and vincristine for the treatment of recurrent small-cell lung cancer. J Clin Oncol 1999; 17: 658–667. https://doi.org/10.1200/JCO.1999.17.2.658

[23] AHN MJ, CHO BC, FELIP E, KORANTZIS I, OHASHI K et al. Tarlatamab for Patients with Previously Treated Small-Cell Lung Cancer. N Engl J Med 2023; 389: 2063–2075. https://doi.org/10.1056/NEJMoa2307980

[24] TRIGO J, SUBBIAH V, BESSE B, MORENO V, LÓPEZ R et al. Lurbinectedin as second-line treatment for patients with small-cell lung cancer: a single-arm, open-label, phase 2 basket trial. Lancet Oncol 2020; 21: 645–654. https://doi.org/10.1016/S1470-2045(20)30068-1

[25] KIM HR, AWAD MM, NAVARRO A, GOTTFRIED M, PETERS S et al. Patient-Reported Health-Related Quality of Life in KEYNOTE-604: Pembrolizumab or Placebo Added to Etoposide and Platinum as First-Line Therapy for Extensive-Stage SCLC. JTO Clin Res Rep 2023; 4: 100572. https://doi.org/10.1016/j.jtocrr.2023.100572

[26] YU G, CAI Q, XU X, SHEN Y, XU K. Anlotinib-containing regimen for advanced small-cell lung cancer: A protocol of meta-analysis. PLoS One 2021; 16: e0247494. https://doi.org/10.1371/journal.pone.0247494

[27] CHUNG HC, PIHA-PAUL SA, LOPEZ-MARTIN J, SCHELLENS JHM, KAO S et al. Pembrolizumab After Two or More Lines of Previous Therapy in Patients With Recurrent or Metastatic SCLC: Results From the KEYNOTE-028 and KEYNOTE-158 Studies. J Thorac Oncol 2020; 15: 618–627. https://doi.org/10.1016/j.jtho.2019.12.109

[28] YU Y, CHEN K, FAN Y. Extensive-stage small-cell lung cancer: Current management and future directions. Int J Cancer 2023; 152: 2243–2256. https://doi.org/10.1002/ijc.34346

[29] ZHU W, GENG Q, PENG H, JIN Z, LI D et al. Efficacy and Safety of Low-Dose Nab-Paclitaxel Plus Tislelizumab in Elderly Patients With Previously Treated Metastatic Non-Small Cell Lung Cancer. Front Oncol 2022; 12: 802467. https://doi.org/10.3389/fonc.2022.802467

[30] HEINHUIS KM, ROS W, KOK M, STEEGHS N, BEIJNEN JH et al. Enhancing antitumor response by combining immune checkpoint inhibitors with chemotherapy in solid tumors. Ann Oncol 2019; 30: 219–235. https://doi.org/10.1093/annonc/mdy551

[31] YIN C, ZOU GR, HE Y, LI J, YAN HW et al. Efficiency and toxicity of nab-paclitaxel and camrelizumab in the second or above line treatment of advanced non-small cell lung cancer: a retrospective cohort study. J Thorac Dis 2023; 15: 1838–1847. https://doi.org/10.21037/jtd-23-387

[32] OWONIKOKO TK, NIU H, NACKAERTS K, CSOCZI T, OSTOROS G et al. Randomized Phase II Study of Paclitaxel plus Alisertib versus Paclitaxel plus Placebo as Second-Line Therapy for SCLC: Primary and Correlative Biomarker Analyses. J Thorac Oncol 2020; 15: 274–287. https://doi.org/10.1016/j.jtho.2019.10.013

[33] SPIGEL DR, VICENTE D, CIULEANU TE, GETTINGER S, PETERS S et al. Second-line nivolumab in relapsed small-cell lung cancer: CheckMate 331(*). Ann Oncol 2021; 32: 631–641. https://doi.org/10.1016/j.annonc.2021.01.071

[34] WIEDEMEYER WR, GAVRILYUK J, SCHAMMEL A, ZHAO X, SARVAIYA H et al. ABBV-011, A Novel, Calicheamicin-Based Antibody-Drug Conjugate, Targets SEZ6 to Eradicate Small Cell Lung Cancer Tumors. Mol Cancer Ther 2022; 21: 986–998. https://doi.org/10.1158/1535-7163.MCT-21-0851

[35] PAZ-ARES L, CHAMPIAT S, LAI WV, IZUMI H, GOVINDAN R et al. Tarlatamab, a First-in-Class DLL3-Targeted Bispecific T-Cell Engager, in Recurrent Small-Cell Lung Cancer: An Open-Label, Phase I Study. J Clin Oncol 2023; 41: 2893–2903. https://doi.org/10.1200/JCO.22.02823

[36] LI S, WANG H. Research Progress on Mechanism and Management of Adverse Drug Reactions of Anlotinib. Drug Des Devel Ther 2023; 17: 3429–3437. https://doi.org/10.2147/DDDT.S426898

[37] CHAN JM, QUINTANAL-VILLALONGA Á, GAO VR, XIE Y, ALLAJ V et al. Signatures of plasticity, metastasis, and immunosuppression in an atlas of human small cell lung cancer. Cancer Cell 2021; 39: 1479–1496.e18. https://doi.org/10.1016/j.ccell.2021.09.008

[38] XUE Y, GAO S, GOU J, YIN T, HE H et al. Platinum-based chemotherapy in combination with PD-1/PD-L1 inhibitors: preclinical and clinical studies and mechanism of action. Expert Opin Drug Deliv 2021; 18: 187–203. https://doi.org/10.1080/17425247.2021.1825376

[39] LU S, WU L, JIAN H, CHENG Y, WANG Q et al. Sintilimab plus chemotherapy for patients with EGFR-mutated non-squamous non-small-cell lung cancer with disease progression after EGFR tyrosine-kinase inhibitor therapy (ORIENT-31): second interim analysis from a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Respir Med 2023; 11: 624–636. https://doi.org/10.1016/S2213-2600(23)00135-2

[40] PETTY WJ, PAZ-ARES L. Emerging Strategies for the Treatment of Small Cell Lung Cancer: A Review. JAMA Oncol 2023; 9: 419–429. https://doi.org/10.1001/jamaoncol.2022.5631