Original Article

Efficacy and safety of anlotinib combined with carboplatin and pemetrexed as first-line induction therapy followed by anlotinib plus pemetrexed as maintenance therapy in *EGFR/ALK* wild-type advanced non-squamous non-small cell lung cancer in China: a multicenter, single-arm trial

Zhen He[1#], Xiuli Yang[2#], Tianjiang Ma[3#], Qiumin Yang[4], Chenghui Zhang[5], Yunfang Chen[6], Pengyuan Wang[7], Armida D'Incecco[8], Giulio Metro[9], Shugo Uematsu[10], Qiming Wang[1]

[1]Department of Internal Medicine, Henan Cancer Hospital, Affiliated Cancer Hospital of Zhengzhou University, Zhengzhou, China; [2]Department of Oncology, The First Affiliated Hospital of Nanyang Medical College, Nanyang, China; [3]Department of Medical Oncology, Luohe Central Hospital, Luohe, China; [4]Department of Oncology, Shangqiu First People's Hospital, Shangqiu, China; [5]Department of Oncology, Nanyang Central Hospital, Nanyang, China; [6]Department of Oncology, Zhumadian Central Hospital, Zhumadian, China; [7]Department of Medical Oncology, Xuchang Central Hospital, Xuchang, China; [8]Medical Oncology Unit, "G. Mazzini" Hospital of Teramo, Teramo, Italy; [9]Medical Oncology, Santa Maria della Misericordia Hospital, Azienda Ospedaliera di Perugia, Perugia, Italy; [10]Respiratory Disease Center, Showa University Northern Yokohama Hospital, Kanagawa, Japan

Contributions: (I) Conception and design: Q Wang, Z He; (II) Administrative support: Q Wang; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: Q Wang, Z He; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work and should be considered as co-first authors.

Correspondence to: Qiming Wang. Henan Cancer Hospital, Affiliated Cancer Hospital of Zhengzhou University, 127 Dongming Road, Zhengzhou, China. Email: qimingwang1006@126.com.

Background: The efficacy and safety of chemotherapy strategies combining the multi-target receptor tyrosine kinase inhibitor in patients with advanced *EGFR/ALK* wild-type non-squamous non-small-cell lung cancer (nsq-NSCLC) are undetermined. We aimed to investigate the efficacy and safety of anlotinib combined with carboplatin/pemetrexed-based chemotherapy followed by maintenance therapy (anlotinib plus pemetrexed) in advanced *EGFR/ALK* wild-type nsq-NSCLC.

Methods: Eligible patients with wild-type *EGFR/ALK* advanced nsq-NSCLC who received first-line therapy in Henan Province from March 2019 to February 2021 were recruited. All patients were treated with anlotinib in combination with carboplatin/pemetrexed-based chemotherapy, followed by maintenance therapy (anlotinib plus pemetrexed). The primary endpoint was progression-free survival (PFS). The secondary endpoints included overall survival (OS), disease control rate (DCR), objective response rate (ORR), and adverse events (AEs). Response and AEs were assessed based on the Response Evaluation Criteria in Solid Tumors (1.1) and National Cancer Institute - Common Terminology Criteria for Adverse Events v.4.0.3, respectively. The follow-up interval for survival was 6 weeks and the safety follow-up was performed until the end of treatment. Kaplan-Meier analysis was used to calculate the median PFS and OS.

Results: Thirty-eight participants with median age of 62 (range, 33–75) years were evaluated. Five participants were still on maintenance therapy until the end of the study. The majority were non-smokers (68.4%). The median follow-up was 13.6 (range, 12.3–14.9) months. The median PFS (mPFS) was 10.5 (95% CI: 4.1, 17.0) months, and the median OS was 23.4 [95% CI: not evaluable (NE), NE] months. The DCR and ORR were 94.7% and 60.5%, respectively. Grade 3 and above treatment-related adverse events (TRAEs) happened to 12 participants. The most common TRAEs were hypertension (23.7%), neutropenia (19.4%), and bone marrow toxicity (10.5%). Seven patients discontinued treatment, including two patients during

induction and five patients during maintenance treatment. No grade 5 TRAE was reported. In the non-smoker participants, the mPFS was 14.5 (95% CI: 4.0–25.0) months.

Conclusions: Anlotinib in combination with carboplatin/pemetrexed-based chemotherapy followed by anlotinib plus pemetrexed as maintenance therapy might be an effective choice in treating patients with wild-type *EGFR/ALK* advanced nsq-NSCLC.

Keywords: Anlotinib; carboplatin; pemetrexed; non-squamous; non-small-cell lung cancer (NSCLC)

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Introduction

Lung cancer is the most common cancer and has the highest mortality rate worldwide (1-3). Among lung cancers, more than 85% are non-small-cell lung cancers (NSCLC) (4), and non-squamous NSCLC (nsq-NSCLC) is the major subtype of NSCLC (5). About 70% of NSCLC patients are already diagnosed in an advanced stage (6). The management of NSCLC includes surgery, chemotherapy, targeted therapy, and radiotherapy (7,8). Genotype-driven targeted therapy should be offered for patients with oncogenic driver mutations since such patients benefit from targeted therapy (7-10).

Literature data showed that patients with driver gene-negative advanced nsq-NSCLC cannot benefit from targeted therapy (11). For these patients, platinum-based doublet chemotherapy has represented the backbone for combination strategies to be tested in clinical trials (6-8,12). Recent data indicate that platinum chemotherapy combined with immune checkpoint inhibitors [such as anti-programmed cell death protein-1 (PD-1)/programmed death-ligand 1 (PD-L1)] is associated with a significantly higher clinical benefit versus chemotherapy alone (13,14). Therefore, chemotherapy strategies combining drugs with different action mechanisms have become a research hotspot in the field of lung cancer.

Doublet chemotherapy using pemetrexed in combination with platinum is the classic treatment regimen for patients with driver gene-negative nsq-NSCLC (6-8), but their progression-free survival (PFS) remains suboptimal. Indeed, the PARAMOUNT study showed that, compared with placebo, pemetrexed treatment in combination with platinum followed by pemetrexed maintenance could effectively improve PFS with relatively good tolerance with a median PFS (mPFS) of 7 months (15). Another study showed that the combination of bevacizumab with doublet chemotherapy was well tolerated, with an mPFS of approximately 8 months (16).

Anlotinib is a multi-target receptor tyrosine kinase inhibitor that inhibits angiogenesis and the transduction of proliferation signals in tumors (17). In the ALTER 0303 trial, anlotinib increased overall survival (OS) and PFS in NSCLC patients as third- or further-line therapy, with a good tolerance profile (18). The previous study also proved that the tyrosine kinase inhibitor combined with doublet chemotherapy is tolerable for the NSCLC patients (19). Anlotinib has already been approved by the China National Medical Products Administration (NMPA) for third-line therapy of driver gene-negative nsq-NSCLC.

Based on these data, we hypothesized that the first-line combination of anlotinib with doublet chemotherapy could also improve the clinical benefits for patients with *EGFR/ALK* wild type nsq-NSCLC. Therefore, this multicenter, single-arm clinical trial (ALTER-L012) aimed to explore the efficacy and safety of anlotinib combined with carboplatin and pemetrexed, followed by anlotinib plus pemetrexed as maintenance therapy for first-line therapy of *EGFR/ALK* wild type advanced nsq-NSCLC. The results could suggest an additional option for *EGFR/ALK* wild-type nsq-NSCLC. We present the following article in accordance with the TREND reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-558/rc).

Methods

Study design and participants

This prospective, multicenter, single-arm, clinical trial enrolled *EGFR* and *ALK* wild-type advanced nsq-NSCLC patients scheduled for first-line therapy from March 2019 to February 2021 from six hospitals (Henan Cancer

Hospital; The First Affiliated Hospital of Nanyang Medical College; Luohe Central Hospital; Shangqiu First People's Hospital; Nanyang Central Hospital; and Zhumadian Central Hospital) in Henan Province, China. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Henan Cancer Hospital (as the lead center, No. 2018115) and all participating hospitals/institutions were informed and agreed the study. All participants signed the informed consent form. The study was registered on ClinicalTrials.gov (No. NCT03790228; December 31, 2018).

The detailed inclusion and exclusion criteria are listed in Table S1.

The main key inclusion criteria included: (I) patients aged 18–75 years old; (II) histologically or pathologically proven locally advanced or advanced nsq-NSCLC or nsq-NSCLC recurrence ≥6 months; (III) at least one measurable target lesion not treated by radiotherapy within the last 3 months, with a maximum diameter of the lesion at baseline ≥10 mm (for lymph nodes, the minimum diameter was ≥15 mm); (IV) life expectancy >6 months; (V) Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0–1; and (VI) adequate hematologic and organ function.

The key exclusion criteria included: (I) histological mixed adenosquamous lung cancer; (II) bone metastasis inducing pathological bone fractures; (III) presence of *EGFR* mutation or *ALK* translocation or *EGFR/ALK* status not determined; (IV) distance from tumor to large blood vessel ≤5 mm in computed tomography (CT) or nuclear magnetic resonance imaging (MRI) scan, or central-type lung cancer invading a local large blood vessel, or cavitated or necrotic tumor; (V) malignant tumors other than NSCLC within 5 years before enrollment; (VI) active brain metastases.

Intervention

In this study, Anlotinib 12 mg once per day (qd) was administered with warm water before breakfast for 2 weeks and a week off, with a three weeks cycle. If drug administration was missed on days 1 to 14 and the time to the next administration was <12 h, the drug should not be taken. Carboplatin (AUC5) was performed in a 3 weeks cycle. Carboplatin treatment was stopped after four cycles induction therapy. Pemetrexed (500 mg/m^2) was administered between days 15 and 21 and continued until disease progression. Support treatment was provided, if necessary. Carboplatin treatment was stopped after four cycles of induction therapy. Maintenance therapy (anlotinib and pemetrexed) was continued until disease progression. Patients received dexamethasone, folic acid, and vitamin B12 supplements as required during treatment. Supportive care treatment was provided as per clinical practice.

The treatment was continued until radiological response or tolerance.

If the patients could not tolerate the treatment and adverse events (AEs) appeared, such as diarrhea or adverse skin responses, the treatment was transiently discontinued. If the symptoms did not resolve within 14 days, the treatment of anlotinib was discontinued permanently. The details of dose reduction are shown in the study protocol.

Imaging follow-up was performed on the 6th and 9th, weeks after the initiation of treatment, then switched to once every 6 weeks. Survival follow-up was performed once every 6 weeks, and the safety follow-up ended when the treatment ended.

Endpoints

The primary efficacy endpoint was PFS, referring to the time from the first drug administration to the date of the first disease progression or death whichever occurred. The secondary efficacy endpoints included OS, disease control rate (DCR), and objective response rate (ORR). OS was defined as the time from the first drug administration to death from any cause. The OS was censored on the date of the last follow-up or the last date confirming the patient was alive. Tumor assessments will be based on the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria. DCR was defined as the percentage of patients with complete response (CR), partial response (PR), or stable disease (SD) for ≥4 weeks in all the assessable patients.

The safety endpoint included treatment-related AEs (TRAEs) assessed according to the National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE) 4.03 criteria.

Statistical analysis

The primary endpoint was PFS. Assuming that, after four cycles of anlotinib combined with carboplatin plus pemetrexed treatment, the mPFS of the maintenance therapy using anlotinib and pemetrexed would be 10 months, while the mPFS of the historical controls was 6 months, and

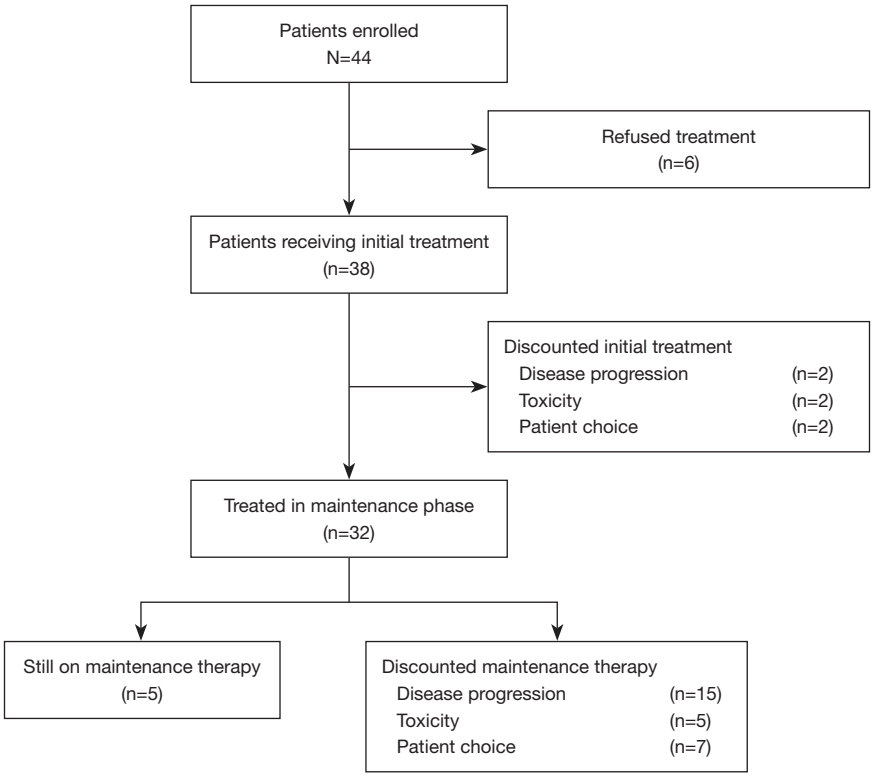

Figure 1 Participant flowchart.

using α=0.05, β=0.2, 12 months of treatment, 12 months of follow-up, and a drop-out rate of 20%, this study planned to include 43 patients.

The continuous data are described as means ± standard deviations or medians (ranges). Categorical data are described as n (%). SAS 9.1.3 (SAS Institute, Cary, NY, USA) was used for the statistical analysis. The Kaplan-Meier method was used to estimate the median OS or PFS, as well as the 95% confidential interval (CI). The analyses are based on the intent-to-treat principle. The full analysis set (FAS) consisted of patients who received the study drugs at least once and had at least one response evaluation. The safety set (SS) consisted of all participants who received at least one dose of study drugs and received safety assessments after drug therapy, regardless of whether they had a response evaluation. The efficacy analysis was performed based on the FAS, and the safety analysis was performed based on the SS. Survival analysis was performed in subgroups stratified by the presence of a gene mutation (detecting by next-generation sequencing; other than *EGFR* and *ALK*, subgroups of *KRAS*, *ERBB*, *TP53*, and *MET* mutations/co-mutations were explored for the potential benefits), sex, stages, smoking, and PS score.

Results

Participant characteristics

A total of 44 participants with wild-type *EGFR/ALK* advanced nsq-NSCLC were enrolled between March 2019 and February 2021. Six participants dropped out without treatment. Thirty-eight participants received the study drugs and received at least one efficacy evaluation and at least one safety assessment, then they were included in both FAS and SS (*Figure 1*). Up to September 20, 2021, nine (23.7%) participants died, 17 (44.7%) patients discontinued treatment due to disease progression, seven (18.4%) discontinued treatment due to AEs, and five (13.2%) were still receiving treatment (*Figure 1*). The median follow-up was 13.6 (range, 12.3–14.9) months. *Table 1* shows demographics and baseline characteristics of patients included in the analysis.

Efficacy

Thirty-eight patients received the initial treatment, and

32 received maintenance therapy (*Figure 1*). The median cycle of maintenance treatment was 9 (range, 1–37). The mPFS of the patients was 10.5 months (95% CI: 4.1, 17.0), and the median OS was 23.4 months [95% CI: not evaluable (NE), NE] (*Figure 2* and Table S2). The DCR and ORR were 94.7% and 60.5%, respectively [complete response (CR) =0, partial response (PR) =23, stable disease (SD) =13, and progression disease (PD) =2] (*Figure 3*, Figure S1, and Table S2).

Table 1 Participant characteristics

Characteristics	Value	%
Median age (years)	62 [33–75]	
Sex		
Male	25	65.8
Female	13	34.2
Pathological stage		
IIIB	6	15.8
IV	32	84.2
Brain metastasis	5	13.2
Smoking status	12	31.6
ECOG PS		
0	11	28.9
1	27	71.1
Driver gene		
Gene mutation	13	34.2
Others + unknowns	25	65.8

ECOG PS, Eastern Cooperative Oncology Group performance status.

Safety

In this study, treatment was discontinued in seven participants due to AEs, and the incidence of therapy discontinuation caused by AEs was 18.4%. *Table 2* shows the TRAEs observed in the SS in this study. No grade 5 AEs occurred. AEs ≥ grade 3 included hypertension in nine participants (23.7%), neutropenia in seven participants (19.4%), bone marrow toxicity in four participants (10.5%), and thrombocytopenia in three participants (7.9%). No patient occurred febrile neutropenia. Two participants had AEs during induction and withdrew from the study, including one with grade 4 thrombocytopenia and one with grade 4 bone marrow toxicity. Five participants experienced AEs during maintenance therapy and dropped out, including two with grade 4 bone marrow toxicity, one with grade 4 weakness, and two with grade 3 neutropenia.

Subgroup analyses

Table 3 shows the subgroup analyses. The mPFS was 13.1 (95% CI: 5.0, 21.2) months in the gene mutation group. For participants with other gene mutations or an unknown gene mutation status, the mPFS was 10.3 (95% CI: 6.5, 14.1) months (Figure S2). The mPFS in male participants was 10.3 (95% CI: 6.1, 14.5) months. The mPFS was 5.7 (95% CI: 4.7, 6.7) and 13.1 (95% CI: 7.8, 18.4) for patients with stage III and IV disease and was 10.3 (95% CI: 3.4, 17.2) and 14.5 (95% CI: 4.0, 25.0) months for smokers and non-smokers, respectively. The ORR was 65.4% in non-smokers. The ORR of the subgroup was shown in *Figure 4*.

Discussion

This trial aimed to explore the efficacy and safety of anlotinib

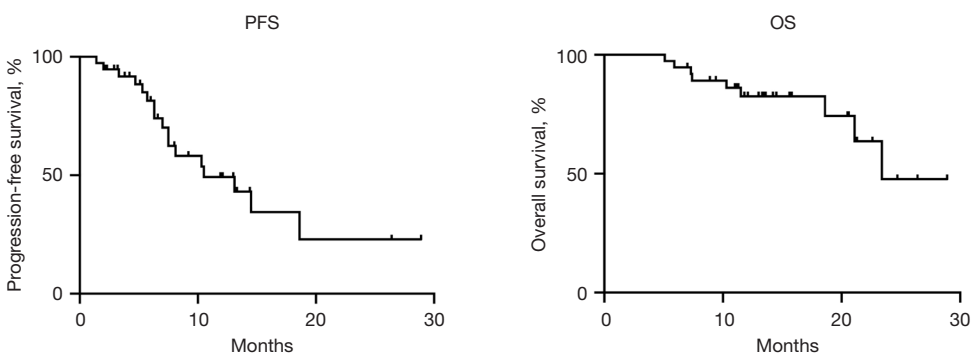

Figure 2 Median PFS and median OS. PFS, progression-free survival; OS, overall survival.

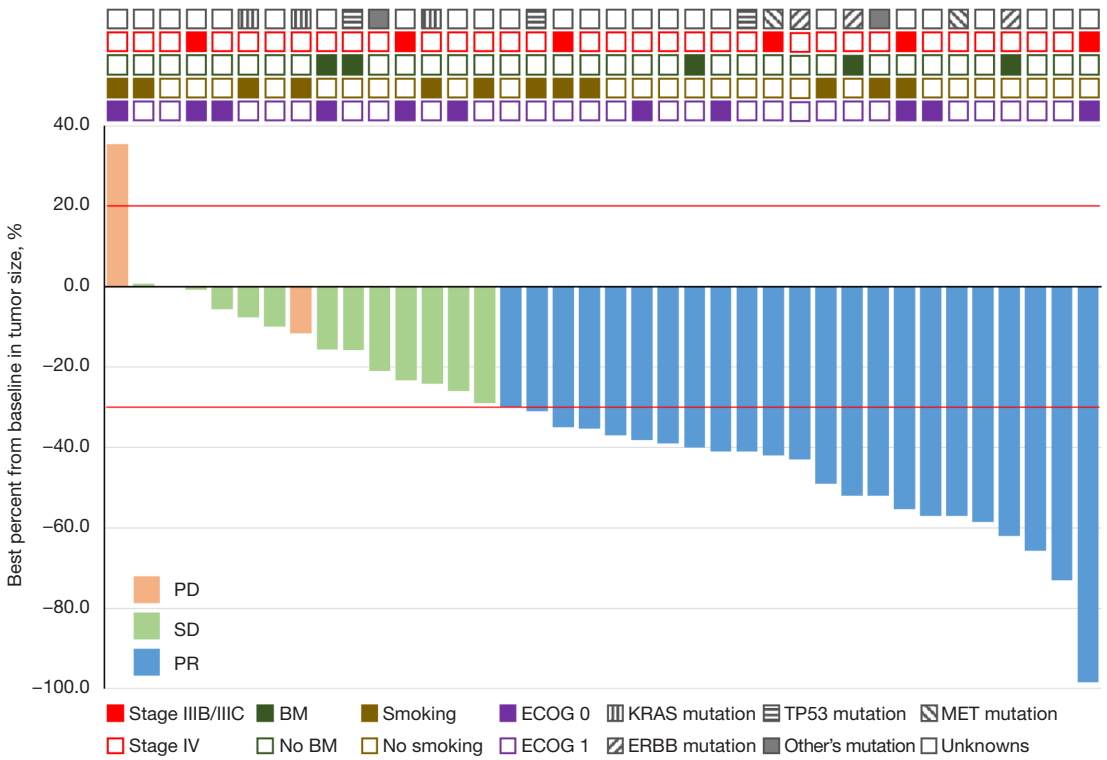

Figure 3 Waterfall plot of treatment response. PD, progression disease; SD, stable disease; PR, partial response; BM, brain metastasis; ECOG, Eastern Cooperative Oncology Group; KRAS, Kirsten rat sarcoma viral oncogene homolog; TP53, tumor protein p53; MET, mesenchymal-epithelial transition factor; ERBB, epidermal growth factor receptor.

combined with carboplatin and pemetrexed, followed by anlotinib combined with pemetrexed maintenance therapy as first-line treatment for advanced *EGFR/ALK* wild type nsq-NSCLC, to our knowledge, this is the first trial of such combination as first-line treatment for NSCLC. The results suggest that anlotinib plus carboplatin and pemetrexed followed by anlotinib plus pemetrexed maintenance therapy might be a promising treatment for patients with *EGFR/ALK* wild-type advanced nsq-NSCLC. It has a potential value for non-smokers, which will have to be confirmed.

The mPFS and OS in this study were 10.5 (95% CI: 4.1, 17.0) and 23.4 (95% CI: NE, NE) months, which appear to be better than chemotherapy alone based on historical data. Indeed, the PARAMOUNT study showed that the mPFS (from induction) of the patients who received maintenance pemetrexed immediately after induction treatment with pemetrexed plus cisplatin for advanced nsq-NSCLC was 6.9 (95% CI: 6.2–7.5) months (15), and the mOS (from induction) was 16.9 (95% CI: 15.8–19.0) months (20). The mPFS in this study was numerically higher than the mPFS achieved with chemotherapy plus bevacizumab; the mPFS of pemetrexed and carboplatin plus bevacizumab with maintenance pemetrexed and bevacizumab as first-line therapy has been reported to be 7.8 (95% CI: 5.2–11.5) months (16).

Immune checkpoint inhibitors are increasingly used in lung cancer (8). The PFS in this study was comparable to that observed in the RATIONALE 304 study (21), in which the mPFS of tislelizumab plus chemotherapy as first-line treatment was 9.7 months (95% CI: 7.7–11.7). In the CameL study (22), the mPFS of camrelizumab plus carboplatin and pemetrexed treatment was 11.3 months (95% CI: 9.6–15.4). The KEYNOTE-021 study (23) demonstrated that pemetrexed and carboplatin with pembrolizumab as the first-line therapy for advanced nsq-NSCLC were effective. Still, the percentage of smokers in the KEYNOTE-021 study was 75%, substantially higher than the 31.6% in the present study. Smokers are more sensitive to immunotherapy (24,25), and thus the results in the two cohorts are not comparable. The findings of the present study could be more applicable to Chinese patients since only Chinese participants were enrolled. Although no direct comparison was made between

Table 2 Adverse events

AE terms	n	%	Grade 1–2		Grade ≥3	
			n	%	n	%
Any TRAE	37	97.4	36	94.7	12	31.6
Neutropenia	20	52.6	13	34.2	7	18.4
Hypertension	19	50.0	10	26.3	9	23.7
Leukopenia	19	50.0	17	44.7	2	5.3
Anemia	15	39.5	12	31.6	2	5.3
Nausea and vomiting	12	32.3	12	32.3	0	0
Thrombocytopenia	10	26.3	7	18.4	3	7.9
TSH elevation	10	26.3	10	26.3	0	0
ALT elevation	9	23.7	9	23.7	0	0
Oral ulcer	9	23.7	8	21.1	1	2.6
AST elevation	9	23.7	9	23.7	0	0
Constipation	9	23.7	9	23.7	0	0
Weakness	9	23.7	8	21.1	1	2.6
Diarrhea	7	18.4	6	16.1	1	2.6
High cholesterol	7	18.4	7	18.4	0	0
Hand foot syndrome	7	18.4	5	13.2	2	5.3
GGT elevation	5	13.2	4	10.5	1	2.6
Headache and dizziness	5	13.2	5	13.2	0	0
Bone marrow toxicity	5	13.2	1	2.6	4	10.5
Lymphocytopenia	5	13.2	3	7.9	2	5.3
Fever	5	13.2	5	13.2	0	0

AE, adverse event; TRAE, treatment-related adverse event; TSH, thyroid stimulating hormone; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutaryl transferase.

immunotherapy and anlotinib, the present study might suggest that anlotinib has benefits similar to immunotherapy in lung cancer patients, adding another option as a treatment line. Whether immunotherapy or anlotinib-based regimens should be given as first-line therapy and the other as second-line remains to be explored in future trials.

The subgroup analysis suggested that anlotinib combined with carboplatin and pemetrexed followed by anlotinib plus pemetrexed maintenance therapy might be more effective in non-smokers. The previous studies found that tobacco can induce PD-L1 expression, and smokers have better responses to immunotherapy (24,25). In the KEYNOTE-021 trial, the ORR of patients with low PD-L1 levels was relatively low (26%), which might be due to the low percentage of non-smokers (<25%) (23). In this study, the ORR of non-smokers was as high as 65.4%. Therefore, the regimen of anlotinib combined with carboplatin and pemetrexed followed by anlotinib plus pemetrexed maintenance therapy might be more suitable for non-smokers or patients with low PD-L1 levels. Unfortunately, PD-L1 levels were not obtained in this trial, and they will have to be examined in future trials. Regarding non-smokers, recent data suggest that never smokers benefit more from chemotherapy combined with immunotherapy rather than immunotherapy only (PD-L1 >50%) (26), while the KEYNOTE-189 trial suggests more benefits of immunotherapy in non-smokers (27). Additional trials are necessary to clarify this issue. A future step could be to examine the benefits derived from chemotherapy combined with anlotinib and immunotherapy for never smokers.

In this study, the mPFS was 13.1 months for patients confirmed with gene mutations other than *EGFR* and *ALK* (i.e., *KRAS*, *ERBB*, *TP53*, and *MET*) and 10.3 months for patients with an unknown gene mutation status. Therefore, for patients with wild-type *EGFR/ALK* but with other gene mutations, anlotinib-based chemotherapy could have higher efficacy than in patients with unknown gene mutation status. However, more studies with larger sample sizes are still needed to clarify the efficacy profile of anlotinib according to specific types of gene mutations.

Regarding safety, the incidence of therapy discontinuation due to AEs was 18.4% to anlotinib and chemotherapy, and the combined therapy regimen was tolerable. No new safety signals were observed in this study. The most common AEs were hypertension, neutropenia, bone marrow toxicity, and thrombocytopenia, in agreement with the known AE profile of anlotinib combined with chemotherapy (17,18,28,29).

To our knowledge, this is the first trial to investigate the efficacy and safety of anlotinib combined with carboplatin and pemetrexed, followed by anlotinib and pemetrexed maintenance therapy in patients with driver gene-negative advanced nsq-NSCLC.

This study had limitations. It was a single-arm, non-randomized trial with no control group. Therefore, comparisons must be performed with other trials, and such comparisons are for indicative purposes only since the characteristics of the study populations and treatment strategies were never exactly the same. In addition, the possible superiority of anlotinib to other antiangiogenic drugs will have to be investigated. Secondly, the sample size of treated patients was relatively small. Finally, all patients

Table 3 Subgroup analysis of PFS

Subgroup	n	Events, n (%)	mPFS	12-month PFS rate (%)
Gene mutation	13	6 (46.2)	13.1 (5.0, 21.2)	46.2
Gene mutation of others and unknown	25	11 (44.0)	10.3 (6.54, 14.1)	20.0
Male	25	13 (52.0)	10.3 (6.1, 14.5)	16.0
Female	13	4 (30.8)	NE	53.8
Pathological stage (IIIB)	6	3 (50.0)	5.7 (4.7, 6.7)	0
Pathological stage (IV)	32	13 (40.6)	13.1 (7.8, 18.4)	34.4
Smokers	12	8 (66.7)	10.3 (3.4, 17.2)	16.7
Non-smokers	26	8 (30.8)	14.5 (4.0, 25.0)	34.6
PS =0	11	7 (36.4)	6.3 (4.6, 8.0)	27.3
PS =1	27	9 (33.3)	13.1 (8.4, 17.8)	29.6

PFS, progression-free survival; mPFS, median progression-free survival; PS, performance status; NE, not evaluable.

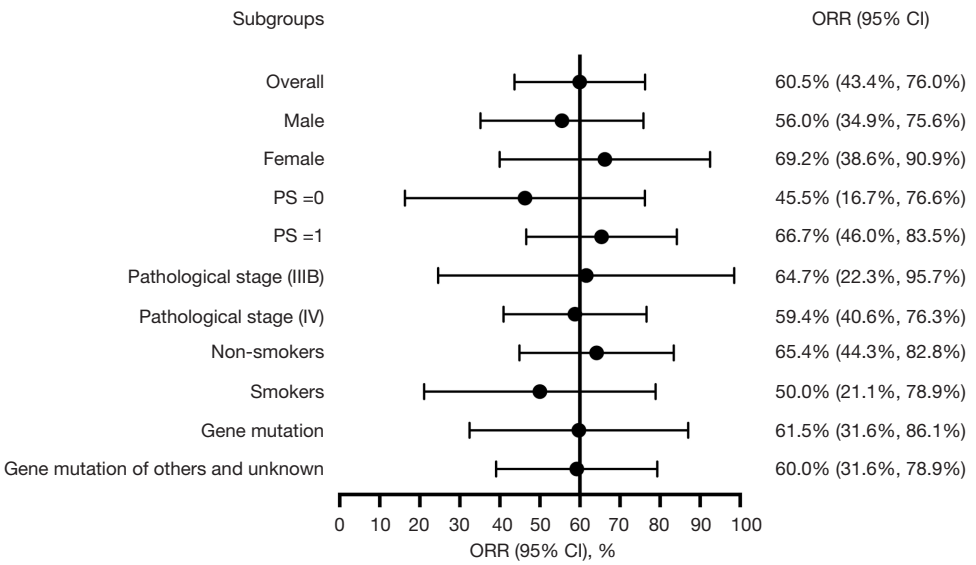

Figure 4 The ORR of the subgroups. ORR, objective response rate; PS, performance status.

were Chinese, thus limiting the generalizability of the results outside China.

In conclusion, the mPFS of anlotinib combined with carboplatin and pemetrexed followed by anlotinib plus pemetrexed maintenance therapy in *EGFR/ALK* wild-type advanced nsq-NSCLC patients appears to be longer than the mPFS of chemotherapy alone (based on historical data). Hence, the efficacy is promising, and the toxicities were tolerable. The findings of this study could provide a new alternative for the treatment of patients with *EGFR/ALK* wild-type advanced nsq-NSCLC. It has a potential value for non-smokers, and anlotinib combined chemo-IO need to be confirmed further.

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Footnote

Reporting Checklist: The authors have completed the TREND reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-558/rc

Data Sharing Statement: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-558/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-558/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Henan Cancer Hospital (No. 2018115). All participating hospitals/institutions were informed and agreed the study. Informed consent was given by all individual participants.

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Supplementary

Table S1 Inclusion and exclusion criteria

Inclusion criteria	• Signed the informed consent form prior to patient entry; • Male or female patients aged 18-75 years old; • Diagnosed with advanced NSCLC (phase IIIB/IV) through pathology, Neoadjuvant chemotherapy, or postoperative adjuvant chemotherapy or neoadjuvant chemotherapy combined with postoperative adjuvant chemotherapy or targeted chemoradiotherapy for local advanced disease recurrence within 6 months after completion; • In the past 3 months at least one target lesion that had not previously been irradiated, and at least one direction with the longest diameter at baseline greater than 10 mm (shorter diameter required not less than 15 mm if lymph nodes are involved) could be imaged by CT scan or MRI; • Expected Survival Time: Over 6 months; • Had an Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 or 1 (on a 5-point scale, with higher scores indicating increasing disability); • The main organs function are normally, the following criteria are met: (1) Blood routine examination criteria should be met (no blood transfusion and blood products within 14 days, no correction by G-CSF and other hematopoietic stimuli): HB ≥90 g/L; ANC ≥ 1.5×10^9/L; PLT ≥80×10^9/L; (2) Biochemical examinations must meet the following criteria: TBIL <1.5×ULN; ALT and AST <2.5×ULN, and for patients with liver metastases <5×ULN; serum Cr ≤1.25×ULN or endogenous creatinine clearance >60 ml/min (Cockcroft-Gault formula); • Women of child-bearing age should take appropriate contraceptive measures and should not breastfeed from screening to 3 months after stopping the study and treatment. Before starting administration, the pregnancy test was negative, or one of the following criteria was met to prove that there was no risk of pregnancy: 1. Post-menopause is defined as amenorrhea at least 12 months after age 50 and cessation of all exogenous hormone replacement therapy; 2. Postmenopausal women under the age of 50 years also be considered postmenopausal if their amenorrhea is 12 months or more after the cessation of all exogenous hormone therapy and their luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels are within the reference value range of laboratory postmenopausal; 3. Has undergone irreversible sterilization surgery, including hysterectomy, bilateral ovariectomy or bilateral salpingectomy, except for bilateral tubal ligation. • For men, consent is required to use appropriate methods of contraception or to be surgically sterilized during the trial and 8 weeks after the last administration of the trial drug.
Exclusion criteria	• Small cell lung cancer (including lung cancer mixed with small cell lung cancer and non-small cell lung cancer), lung sarcomatoid carcinoma; • Had histologically confirmed lung squamous cell carcinoma, or adenosquamous carcinoma; • Patients with pathological fracture in bone metastasis of non-small-cell lung cancer; • Tumor histology or cytology confirmed EGFR mutagenesis [EGFR sensitive mutations include 18 exon point mutations (G719X), 19 exon deletions, 20 exon S768I mutations and 21 exon point mutations (L858R and L861Q)] and ALK gene rearrangement positivity, include EGFR/ALK status cannot be determined for various reasons; • Imaging (CT or MRI) shows that the distance between tumor lesion and the large blood vessel is ≤ 5 mm, or there is a central tumor that invades the local large blood vessel; or there is a significant pulmonary cavity or necrotizing tumor; • Medical history and combined history: 1. Active brain metastases, cancerous meningitis, spinal cord compression, or imaging CT or MRI screening for brain or pia mater disease (a patient with brain metastases who have completed treatment and stable symptoms in 28 days before enrollment may be enrolled, but should be confirmed by brain MRI, CT or venography evaluation as no cerebral hemorrhage symptoms and metastases in midbrain, pons, cerebellum, medulla oblongata, or spinal cord, brain metastases and local radiotherapy after two weeks to allow group); 2. The patient is participating in other clinical studies or completing the previous clinical study in less than 4 weeks; 3. Had malignant tumors except NSCLC within 5 years before enrollment (except for patients with cervical carcinoma *in situ*, basal cell or squamous cell skin cancer who have undergone a curative treatment, local prostate cancer after radical resection, ductal carcinoma *in situ* or papillary thyroid cancer after radical resection); 4. Abnormal blood coagulation (INR >1.5 or prothrombin time (PT) >ULN + 4 seconds or APTT >1.5 ULN), with bleeding tendency or undergoing thrombolytic or anticoagulant therapy; Note: Under the premise of prothrombin time international normalized ratio (INR) ≤ .5, low-dose heparin (adult daily dose of 0.6 million to 12,000 U) or low-dose aspirin (daily dosage ≤100 mg) is allowed for preventive purposes; 5. Renal insufficiency: urine routine indicates urinary protein ≥++, or confirmed 24-hour urine protein ≥ 1.0g; 6. The effects of surgery or trauma have been eliminated for less than 14 days before enrollment in subjects who have undergone major surgery or have severe trauma; 7. Severe acute or chronic infections requiring systemic treatment; 8. Suffering from severe cardiovascular disease: myocardial ischemia or myocardial infarction above grade II, poorly controlled arrhythmias (including men with QTc interval ≥450 ms, women ≥470 ms); according to NYHA criteria, grades III to IV Insufficient function, or cardiac color Doppler ultrasound examination indicates left ventricular ejection fraction (LVEF) <50%; 9. There is currently a peripheral neuropathy of CTCAE ≥2 degrees, except for trauma; 10. Respiratory syndrome (CTC AE grade ≥2 dyspnea), serous effusion (including pleural effusion, ascites, pericardial effusion) requiring surgical treatment; 11. Long-term unhealed wounds or fractures; 12. Decompensated diabetes or other ailments treated with high doses of glucocorticoids; 13. Factors that have a significant impact on oral drug absorption, such as inability to swallow, chronic diarrhea, and intestinal obstruction; 14. Clinically significant hemoptysis (daily hemoptysis greater than 50ml) within 3 months prior to enrollment; or significant clinically significant bleeding symptoms or defined bleeding tendency, such as gastrointestinal bleeding, hemorrhagic gastric ulcer, baseline fecal occult blood ++ and above, or suffering from vasculitis; 15. Events of venous/venous thrombosis occurring within the first 12 months prior to enrollment, such as cerebrovascular accidents (including transient ischemic attacks, cerebral hemorrhage, cerebral infarction), deep vein thrombosis, and pulmonary embolism; • Physical examination and laboratory findings: 1. A known history of HIV testing positive or acquired immunodeficiency syndrome (AIDS); 2. Untreated active hepatitis (hepatitis b: HBsAg positive and HBV DNA more than 1×10^3 copy /ml; Hepatitis c: HCV RNA is positive and liver function is abnormal); Combined with hepatitis b and hepatitis c infection; 3. Serious diseases that endanger patients' safety or affect patients' completion of research, according to the researchers' judgment.

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Table S2 Treatment outcomes

Best response	Patients (n=38)	
	n	%
Complete response	0	0
Partial response	23	60.5%
Stable disease	13	34.2%
Progressive disease	2	5.3%
Objective response rate	60.5%	
95%CI	43.4%-76.0%	
Disease control rate	94.7%	
95%CI	82.3%-99.4%	
Median progression-free survival, months	10.5	
95%CI	4.1-17.0	
Median overall survival, months	23.4	
95%CI	NE-NE	

CI: confidence interval; NE: non-evaluable.

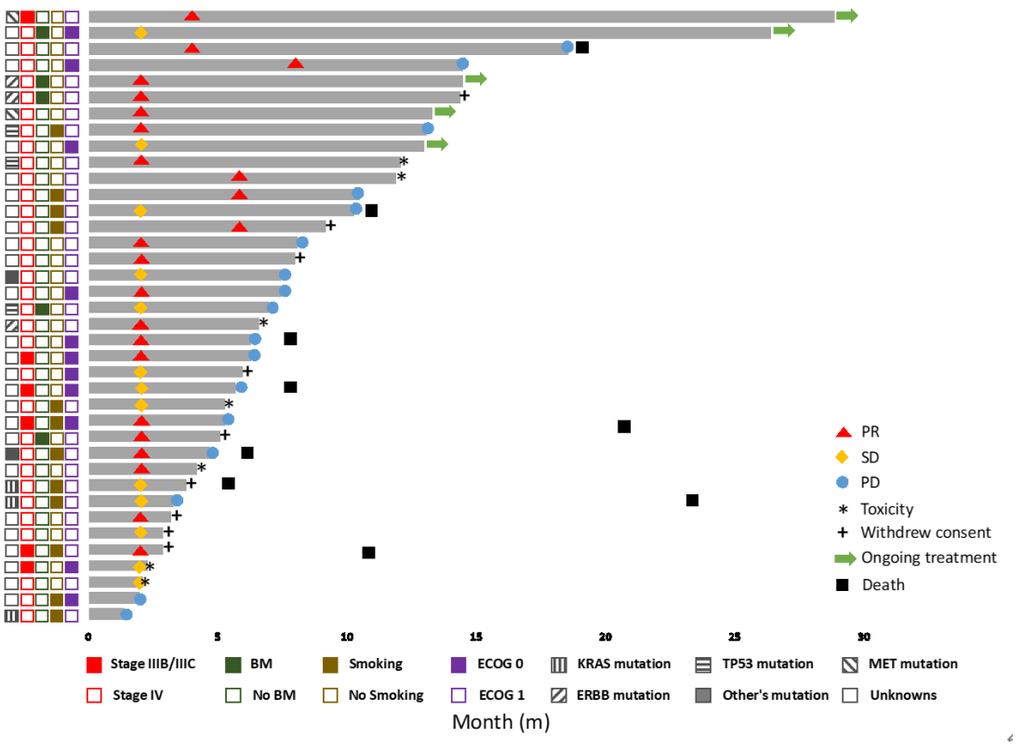

Figure S1 Swimlane chart of the time-to-event.

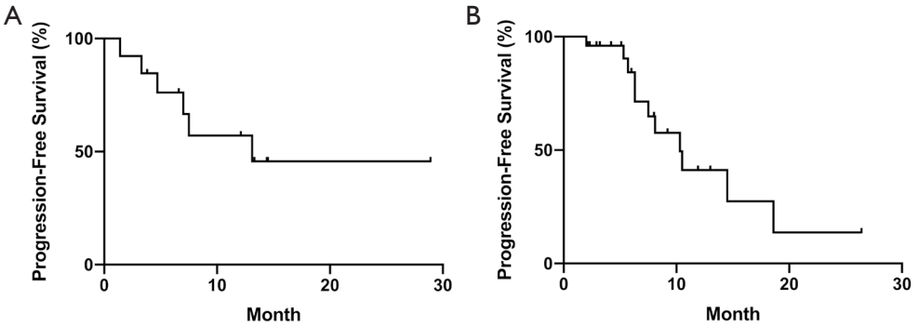

Figure S2 Kaplan-Meier curves of progression-free survival for patients with (A) other gene mutations (B) unknown gene mutation status.

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