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

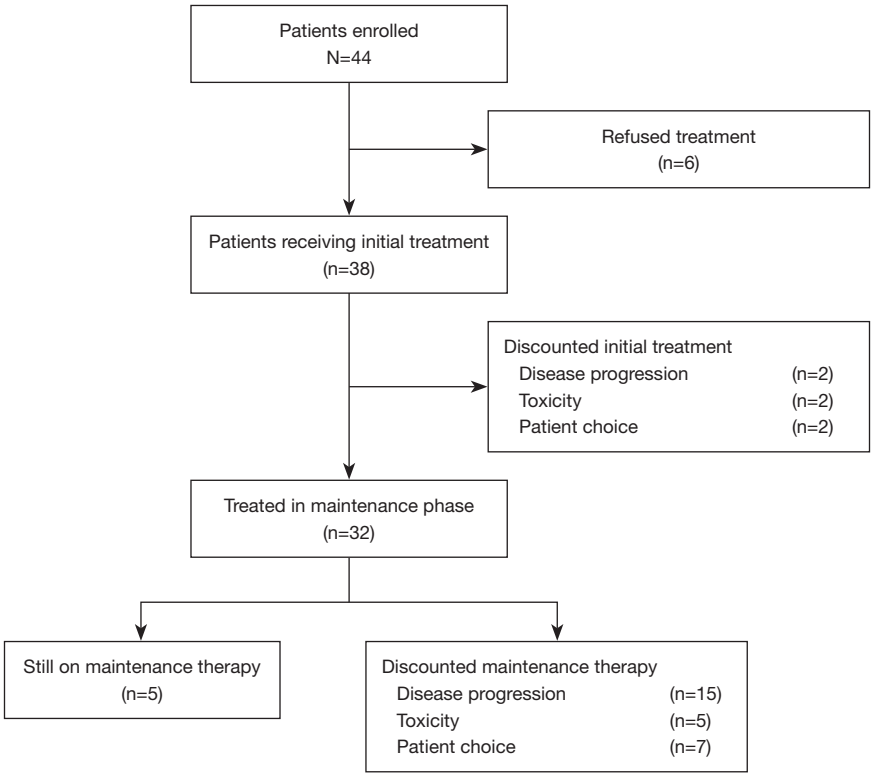

Figure 1 Participant flowchart.

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

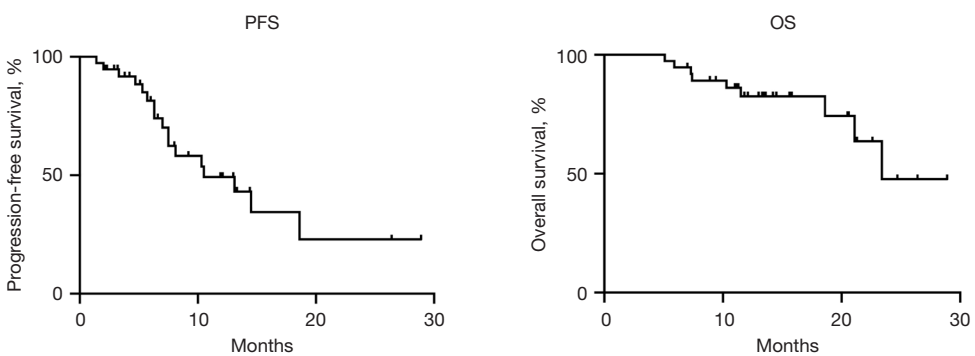

Figure 2 Median PFS and median OS. PFS, progression-free survival; OS, overall survival.

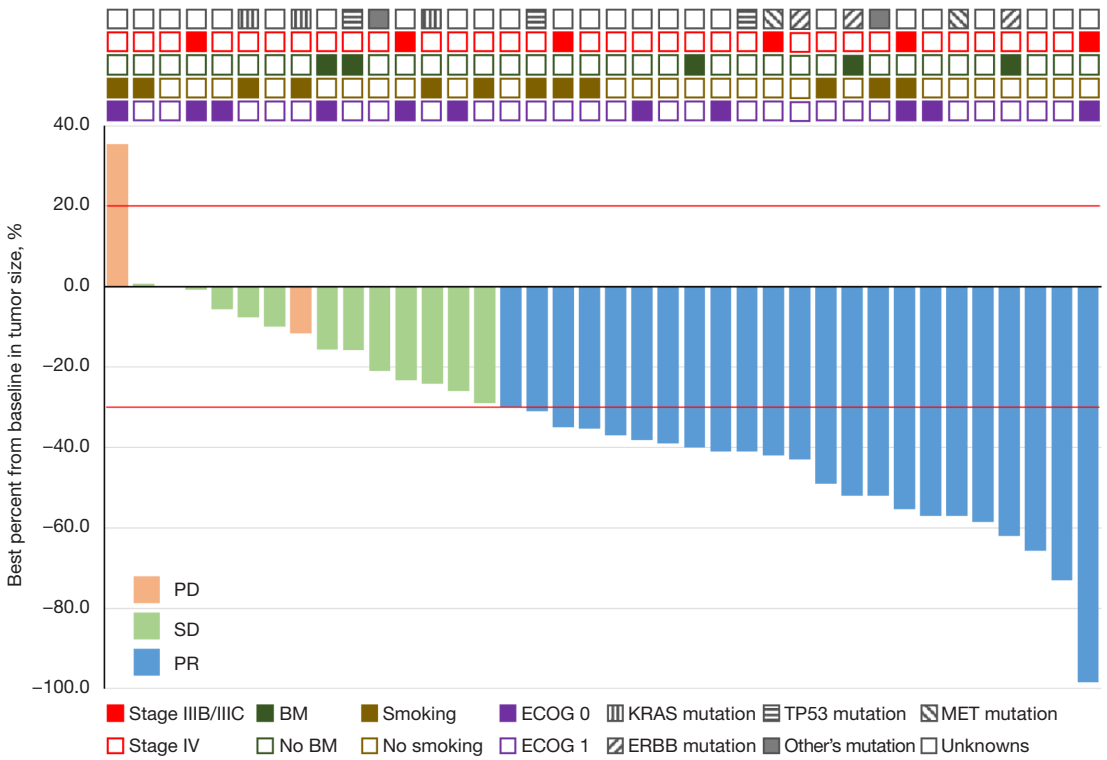

Figure 3 Waterfall plot of treatment response. PD, progression disease; SD, stable disease; PR, partial response; BM, brain metastasis; ECOG, Eastern Cooperative Oncology Group; KRAS, Kirsten rat sarcoma viral oncogene homolog; TP53, tumor protein p53; MET, mesenchymal-epithelial transition factor; ERBB,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

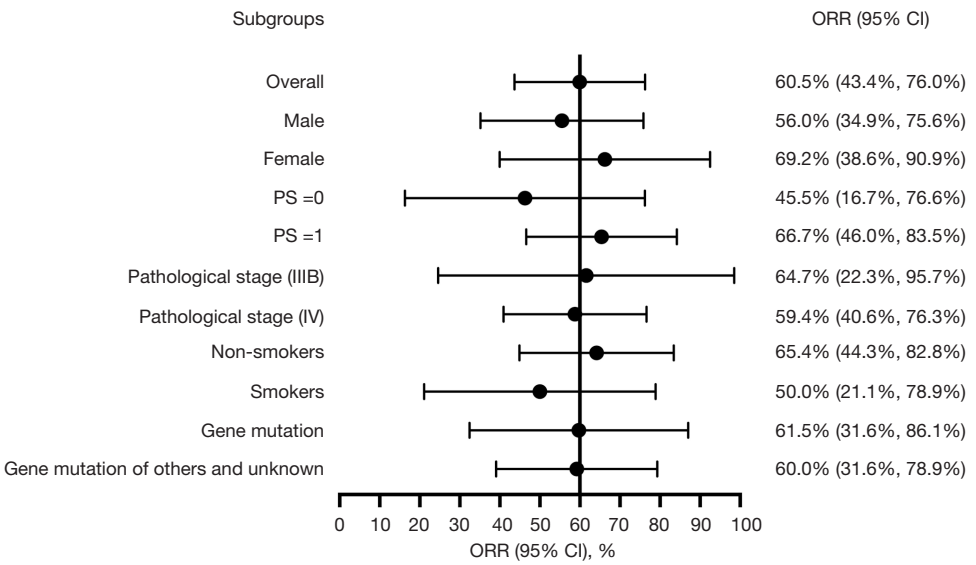

Figure 4 The ORR of the subgroups. ORR, objective response rate; PS, performance status.

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.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021;71:209-49.
2. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424.
3. Siegel RL, Miller KD, Fuchs HE, et al. Cancer Statistics, 2021. CA Cancer J Clin 2021;71:7-33.
4. Herbst RS, Morgensztern D, Boshoff C. The biology and management of non-small cell lung cancer. Nature 2018;553:446-54.
5. Barta JA, Powell CA, Wisnivesky JP. Global Epidemiology of Lung Cancer. Ann Glob Health 2019;85:8.
6. Besse B, Adjei A, Baas P, et al. 2nd ESMO Consensus Conference on Lung Cancer: non-small-cell lung cancer first-line/second and further lines of treatment in advanced disease. Ann Oncol 2014;25:1475-84.
7. Novello S, Barlesi F, Califano R, et al. Metastatic non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2016;27:v1-v27.
8. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Non-Small Cell Lung Cancer. Version 3.2022. Fort Washington: National Comprehensive Cancer Network; 2022.
9. Shea M, Costa DB, Rangachari D. Management of advanced non-small cell lung cancers with known mutations or rearrangements: latest evidence and treatment approaches. Ther Adv Respir Dis 2016;10:113-29.
10. Lindeman NI, Cagle PT, Aisner DL, et al. Updated Molecular Testing Guideline for the Selection of Lung Cancer Patients for Treatment With Targeted Tyrosine Kinase Inhibitors: Guideline From the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology. Arch Pathol Lab Med 2018;142:321-46.
11. Lamberti G, Andrini E, Sisi M, et al. Beyond EGFR, ALK and ROS1: Current evidence and future perspectives on newly targetable oncogenic drivers in lung adenocarcinoma. Crit Rev Oncol Hematol 2020;156:103119.
12. Wu YL, Lu S, Cheng Y, et al. Efficacy and safety of pemetrexed/cisplatin versus gemcitabine/cisplatin as first-line treatment in Chinese patients with advanced

nonsquamous non-small cell lung cancer. Lung Cancer 2014;85:401-7.
13. Paz-Ares L, Luft A, Vicente D, et al. Pembrolizumab plus Chemotherapy for Squamous Non-Small-Cell Lung Cancer. N Engl J Med 2018;379:2040-51.
14. West H, McCleod M, Hussein M, et al. Atezolizumab in combination with carboplatin plus nab-paclitaxel chemotherapy compared with chemotherapy alone as first-line treatment for metastatic non-squamous non-small-cell lung cancer (IMpower130): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol 2019;20:924-37.
15. Paz-Ares L, de Marinis F, Dediu M, et al. Maintenance therapy with pemetrexed plus best supportive care versus placebo plus best supportive care after induction therapy with pemetrexed plus cisplatin for advanced non-squamous non-small-cell lung cancer (PARAMOUNT): a double-blind, phase 3, randomised controlled trial. Lancet Oncol 2012;13:247-55.
16. Patel JD, Hensing TA, Rademaker A, et al. Phase II study of pemetrexed and carboplatin plus bevacizumab with maintenance pemetrexed and bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer. J Clin Oncol 2009;27:3284-9.
17. Sun Y, Niu W, Du F, et al. Safety, pharmacokinetics, and antitumor properties of anlotinib, an oral multi-target tyrosine kinase inhibitor, in patients with advanced refractory solid tumors. J Hematol Oncol 2016;9:105.
18. Han B, Li K, Wang Q, et al. Effect of Anlotinib as a Third-Line or Further Treatment on Overall Survival of Patients With Advanced Non-Small Cell Lung Cancer: The ALTER 0303 Phase 3 Randomized Clinical Trial. JAMA Oncol 2018;4:1569-75.
19. Tanaka K, Asahina H, Kishimoto J, et al. Osimertinib versus osimertinib plus chemotherapy for non-small cell lung cancer with EGFR (T790M)-associated resistance to initial EGFR inhibitor treatment: An open-label, randomised phase 2 clinical trial. Eur J Cancer 2021;149:14-22.
20. Paz-Ares LG, de Marinis F, Dediu M, et al. PARAMOUNT: Final overall survival results of the phase III study of maintenance pemetrexed versus placebo immediately after induction treatment with pemetrexed plus cisplatin for advanced nonsquamous non-small-cell lung cancer. J Clin Oncol 2013;31:2895-902.
21. Lu S, Wang J, Yu Y, et al. Tislelizumab Plus Chemotherapy as First-Line Treatment for Locally Advanced or Metastatic Nonsquamous NSCLC (RATIONALE 304): A Randomized Phase 3 Trial. J Thorac Oncol 2021;16:1512-22.
22. Zhou C, Chen G, Huang Y, et al. Camrelizumab plus carboplatin and pemetrexed versus chemotherapy alone in chemotherapy-naive patients with advanced non-squamous non-small-cell lung cancer (CameL): a randomised, open-label, multicentre, phase 3 trial. Lancet Respir Med 2021;9:305-14.
23. Langer CJ, Gadgeel SM, Borghaei H, et al. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. Lancet Oncol 2016;17:1497-508.
24. Dai L, Jin B, Liu T, et al. The effect of smoking status on efficacy of immune checkpoint inhibitors in metastatic non-small cell lung cancer: A systematic review and meta-analysis. EClinicalMedicine 2021;38:100990.
25. Jain E, Sharma S, Aggarwal A, et al. PD-L1 expression and its clinicopathologic and genomic correlation in the non-small cell lung carcinoma patients: An Indian perspective. Pathol Res Pract 2021;228:153497.
26. Akinboro O, Vallejo JJ, Nakajima EC, et al. Outcomes of anti–PD-(L)1 therapy with or without chemotherapy (chemo) for first-line (1L) treatment of advanced non–small cell lung cancer (NSCLC) with PD-L1 score ≥ 50%: FDA pooled analysis. J Clin Oncol 2022;40:9000.
27. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. N Engl J Med 2018;378:2078-92.
28. Si X, Zhang L, Wang H, et al. Management of anlotinib-related adverse events in patients with advanced non-small cell lung cancer: Experiences in ALTER-0303. Thorac Cancer 2019;10:551-6.
29. Zhong Q, Liu Z. Efficacy and Safety of Anlotinib in Patients with Advanced Non-Small Cell Lung Cancer: A Real-World Study. Cancer Manag Res 2021;13:4115-28.

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