

Effect of Anlotinib as a Third-Line or Further Treatment on Overall Survival of Patients With Advanced Non-Small Cell Lung Cancer

The ALTER O303 Phase 3 Randomized Clinical Trial

Baohui Han, MD; Kai Li, MD; Qiming Wang, MD; Li Zhang, MD; Jianhua Shi, MD; Zehai Wang, MD; Ying Cheng, MD; Jianxing He, MD; Yuankai Shi, MD; Yizhuo Zhao, MD; Hao Yu, MD; Yang Zhao, MD; Weiqiang Chen, MD; Yi Luo, MD; Lin Wu, MD; Xiuwen Wang, MD; Robert Pirker, MD; Kejun Nan, MD; Faguang Jin, MD; Jian Dong, MD; Baolan Li, MD; Yan Sun, MD

[+ Supplemental content](#)

IMPORTANCE Anlotinib is a novel multitarget tyrosine kinase inhibitor for tumor angiogenesis and proliferative signaling. A phase 2 trial showed anlotinib to improve progression-free survival with a potential benefit of overall survival, leading to the phase 3 trial to confirm the drug's efficacy in advanced non-small cell lung cancer (NSCLC).

OBJECTIVE To investigate the efficacy of anlotinib on overall survival of patients with advanced NSCLC progressing after second-line or further treatment.

DESIGN, SETTING, AND PARTICIPANTS The ALTER O303 trial was a multicenter, double-blind, phase 3 randomized clinical trial designed to evaluate the efficacy and safety of anlotinib in patients with advanced NSCLC. Patients from 31 grade-A tertiary hospitals in China were enrolled between March 1, 2015, and August 31, 2016. Those aged 18 to 75 years who had histologically or cytologically confirmed NSCLC were eligible (n = 606), and those who had centrally located squamous cell carcinoma with cavitory features or brain metastases that were uncontrolled or controlled for less than 2 months were excluded. Patients (n = 440) were randomly assigned in a 2-to-1 ratio to receive either 12 mg/d of anlotinib or a matched placebo. All cases were treated with study drugs at least once in accordance with the intention-to-treat principle.

MAIN OUTCOMES AND MEASURES The primary end point was overall survival. The secondary end points were progression-free survival, objective response rate, disease control rate, quality of life, and safety.

RESULTS In total, 439 patients were randomized, 296 to the anlotinib group (106 [36.1%] were female and 188 [64.0%] were male, with a mean [SD] age of 57.9 [9.1] years) and 143 to the placebo group (46 [32.2%] were female and 97 [67.8%] were male, with a mean [SD] age of 56.8 [9.1] years). Overall survival was significantly longer in the anlotinib group (median, 9.6 months; 95% CI, 8.2-10.6) than the placebo group (median, 6.3 months; 95% CI, 5.0-8.1), with a hazard ratio (HR) of 0.68 (95% CI, 0.54-0.87; $P = .002$). A substantial increase in progression-free survival was noted in the anlotinib group compared with the placebo group (median, 5.4 months [95% CI, 4.4-5.6] vs 1.4 months [95% CI, 1.1-1.5]; HR, 0.25 [95% CI, 0.19-0.31]; $P < .001$). Considerable improvement in objective response rate and disease control rate was observed in the anlotinib group over the placebo group. The most common grade 3 or higher adverse events in the anlotinib arm were hypertension and hyponatremia.

CONCLUSIONS AND RELEVANCE Among the Chinese patients in this trial, anlotinib appears to lead to prolonged overall survival and progression-free survival. This finding suggests that anlotinib is well tolerated and is a potential third-line or further therapy for patients with advanced NSCLC.

TRIAL REGISTRATION ClinicalTrials.gov identifier: [NCT02388919](#)

JAMA Oncol. doi:10.1001/jamaoncol.2018.3039
Published online August 9, 2018.

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Authors: Baohui Han, MD, Shanghai Chest Hospital, Shanghai Jiaotong University, Shanghai 200030, China (xkyyhan@gmail.com); Kai Li, MD, Tianjin Medical University Cancer Institute & Hospital, Huan-Hu-Xi Rd, Tianjin 300060, China (likai5@medmail.com.cn).

Lung cancer is the most commonly diagnosed cancer and accounts for 20% of cancer-related mortality worldwide.¹ An estimated 610 200 patients (22% of cancer-related mortality) died from lung cancer in 2015 in China.² Non-small cell lung cancer (NSCLC) comprises 80% to 85% of lung cancers, and most patients present with locally advanced or metastatic disease at time of diagnosis.³ Recent advancements in the understanding of NSCLC malignant neoplasm molecular pathways have led to the development of targeted therapeutics.⁴⁻⁶ With the advent of novel treatments, such as targeted therapy, it is becoming increasingly common for patients to control their disease through multiple lines of therapy.

Anlotinib (AL3818) hydrochloride is a novel multitarget tyrosine kinase inhibitor (TKI) for tumor angiogenesis and proliferative signaling.⁷ The prime targets of anlotinib include receptor tyrosine kinases vascular endothelial growth factor receptor 1 to 3, endothelial growth factor receptor (EGFR), fibroblast growth factor receptor 1 to 4, platelet-derived growth factor receptor α and β , and stem cell factor receptor.⁷⁻⁹ In phase 2 of the ALTER randomized clinical trial, 117 patients with advanced NSCLC who progressed after second-line or further treatment were enrolled from 13 centers; 60 of these patients were assigned to the anlotinib arm and 57 patients to the placebo arm. An improvement in the primary end point of progression-free survival (PFS) was observed (median PFS, 4.8 months for anlotinib arm vs 1.2 months for placebo arm; hazard ratio [HR], 0.32; $P < .001$), with potential benefit in the secondary end point of overall survival (OS) (median OS, 9.3 months for anlotinib arm vs 6.3 months for placebo arm; $P = .08$).¹⁰ Therefore, we conducted a multicenter, double-blind, randomized phase 3 of the ALTER trial to confirm the efficacy of anlotinib as a third-line or further treatment in patients with advanced NSCLC (stage IIIB to IV). Overall survival was the primary end point of the phase 3 study.

Methods

Study Design

This multicenter, double-blind, randomized phase 3 clinical trial was designed to evaluate the efficacy and safety of anlotinib in patients with advanced NSCLC (ClinicalTrials.gov identifier: NCT02388919). Patients from 31 grade-A tertiary hospitals in China were enrolled between March 1, 2015, and August 31, 2016. All patients provided written informed consent before entering the trial. The trial was conducted according to the principles of the Declaration of Helsinki¹¹ and Good Clinical Practice requirements. All 31 institutions obtained approval from the research ethics board of each site. See Supplement 1 for the trial protocol.

Patients

Eligible patients included those aged 18 to 75 years who had histologically or cytologically confirmed NSCLC. Other inclusion criteria were an Eastern Cooperative Oncology Group Performance Status score of 0 or 1 (score range: 0-5, with the highest score indicating death); life expectancy of 3 months or more; and disease progression after at least 1 line of

Key Points

Question Does anlotinib improve overall survival and progression-free survival in third-line or further treatment of advanced non-small cell lung cancer?

Findings In this randomized clinical trial that included 437 patients with advanced non-small cell lung cancer, substantial improvement in overall survival and progression-free survival was noted in patients who received anlotinib compared with those given placebo. Substantial improvement in objective response rate and disease control rate was also observed among the anlotinib group.

Meaning In third-line or further treatment of Chinese patients with advanced non-small cell lung cancer, anlotinib prolonged overall survival, suggesting that anlotinib is well tolerated and is a potential later therapy for patients with this disease.

chemotherapy and TKI therapy for all patients with driver alterations (*EGFR* [OMIM 131550] mutation or *ALK* [OMIM 105590] rearrangement) as well as disease progression after at least 2 lines of chemotherapy for all patients without driver alterations. Patients were excluded if they had centrally located squamous cell carcinoma with cavitory features or brain metastases that were uncontrolled or controlled for less than 2 months. The full list of inclusion and exclusion criteria are listed in eTable 1 in Supplement 2. See Figure 1 for the patient diagram.

Randomization and Masking

Patients were randomly assigned in a 2-to-1 ratio to receive anlotinib or placebo with a block randomization scheme (block size of 4) using a double-blind, computerized, randomized list generator. Predefined stratification factors were as follows: histopathological classification (adenocarcinoma or squamous cell carcinoma or others), number of metastases (≤ 3 or > 3), driver alterations (*EGFR* mutation or *ALK* rearrangement), and alterations status (positive or negative). Packaging of the anlotinib and placebo pills (supplied by Chia Tai Tianqing Pharmaceutical Group Co, Ltd) was identical and coded according to a random code list.

Procedures

Oral anlotinib (12 mg/d) or matched placebo was administered. Each cycle was defined as 2 weeks on-treatment followed by 1 week off-treatment.⁷ The treatment continued until disease progression or treatment intolerance. Dose modifications (10 mg/d or 8 mg/d) of anlotinib were allowed according to the protocol-defined dose modification criteria. Briefly, if the patient could not tolerate 12 mg/d, then the dose could be reduced to 10 mg/d or 8 mg/d. If the dose of 8 mg/d was not tolerated, then treatment was terminated. In accordance with the Response Evaluation Criteria in Solid Tumors guidelines, version 1.1, tumor assessment was performed using computed tomography within 2 weeks before treatment started. After the treatment initiation, tumors were evaluated once per cycle during the first 2 cycles and then assessed once every 2 cycles. Patient follow-up was done every 8 weeks to assess clinical outcomes, including toxicity, efficacy, and survival, until the death of the patient or until the data cutoff date (January 6, 2017), whichever came first.

Outcomes

The primary end point was OS. The secondary end points were PFS, objective response rate, disease control rate, and quality of life. Patient-reported quality of life was assessed using the European Organisation for Research and Treatment of Cancer questionnaires QLQ-C30 and QLQ-LC13 at every visit before any study-related procedures were conducted. The safety of the treatment was evaluated by the occurrence of adverse events, and the severity of the adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.02.

Statistical Analysis

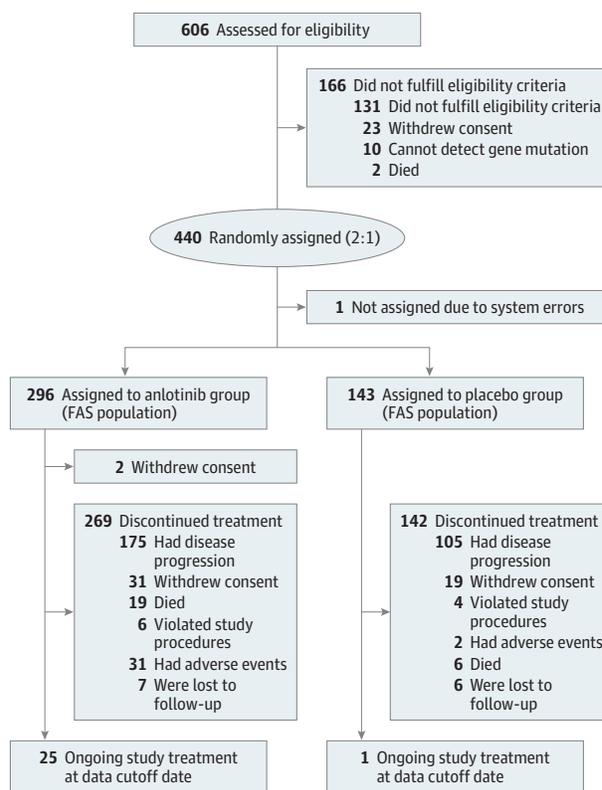
The sample size was calculated on the basis of the following: an HR of 0.70 for the OS with 2-to-1 randomization; a median OS of 11.0 months for the anlotinib group vs 7.0 months for the placebo group according to results from the phase 2 trial; a significance level of $P = .05$; and a statistical power of 85%, with both scheduled accrual and follow-up for 12 months. A total of 450 patients were needed to be enrolled within the scheduled accrual and follow-up to achieve 291 death events.

We assessed the efficacy in the full analysis set, which was defined as all cases treated with study drugs at least once in accordance with the intention-to-treat principle. The survival curves for OS and PFS were estimated with the Kaplan-Meier method and were compared between treatment and control groups using the log-rank test. Changes in QLQ-C30 and QLQ-LC13 questionnaire scores from baseline scores were assessed by Wilcoxon rank sum test. Prespecified subgroup analysis was undertaken using univariate Cox proportional hazards regression models that, along with an interaction term (treatment and subgroup variable), tested the heterogeneity of the anlotinib and placebo subgroups. Objective response rate and disease control rate for each group were compared using Pearson χ^2 or Fisher exact test when appropriate. All statistical tests were carried out on the basis of a 2-sided $\alpha = .05$ and 95% CI.¹² All analyses were performed using SAS software, version 9.4 (SAS Institute Inc).

Results

Of the 606 patients screened for eligibility, 440 patients (72.6%) were enrolled. After enrollment, 1 patient (0.2%) was not assigned because of randomization system error. Overall, 439 patients were randomly assigned to either the anlotinib group ($n = 296$, of whom 106 [36.1%] were female and 188 [64.0%] were male, with a mean [SD] age of 57.9 [9.1] years) or the placebo group ($n = 143$, of whom 46 [32.2%] were female and 97 [67.8%] were male, with a mean [SD] age of 56.8 [9.1] years), but 2 patients in the anlotinib group withdrew their consent after randomization. Five patients did not fulfill eligibility criteria, but according to the intention-to-treat principle and blind review, these patients were not excluded from the full analysis set (Figure 1). The major driver alterations were *EGFR* mutations. Of the 437 patients, 138 (31.6%) exhibited *EGFR* mutations and only 7 (1.6%) harbored the *ALK* rearrangements. The baseline patient information is shown in eTable 2 in

Figure 1. Study Flowchart



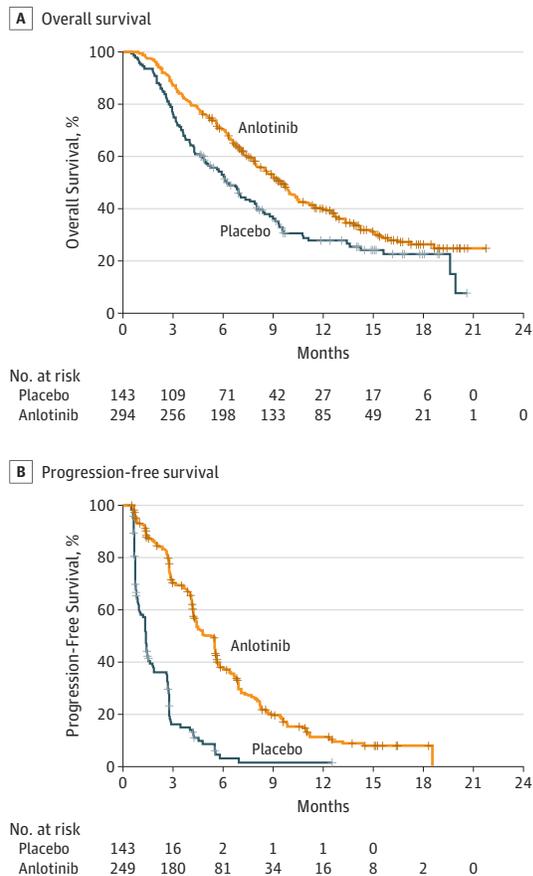
FAS indicates full analysis set. The data cutoff date was January 6, 2017.

Supplement 2, and baseline characteristics were well balanced across the 2 groups.

The median duration of anlotinib treatment was 18 weeks, and the median duration of the placebo treatment was 6 weeks. The median (range) follow-up duration for the anlotinib group was 8.1 (0.9-22.1) months and for the placebo group was 6.0 (0.5-21.0) months.

All 437 patients were included in the efficacy analysis. At the time of data cutoff, 189 of 294 patients (64.3%) in the anlotinib group died compared with the 103 of 143 patients (72.0%) in the placebo group who died. The survival rates of patients in the anlotinib group were 70.6% (95% CI, 65.4%-75.8%) at 6 months, 40.0% (95% CI, 34.0%-46.0%) at 12 months, and 26.2% (95% CI, 20.1%-32.3%) at 18 months. For those in the placebo group, the survival rates were 52.8% (95% CI, 44.6%-61.1%) at 6 months, 27.8% (95% CI, 19.9%-35.7%) at 12 months, and 22.7% (95% CI, 14.8%-30.7%) at 18 months. The median OS was 9.6 months (95% CI, 8.2-10.6) for the anlotinib group (eFigure 4 in Supplement 2), which was substantially longer than the median OS for the placebo group (6.3 months [95% CI, 5.0-8.1]; HR, 0.68 [95% CI, 0.54-0.87]; $P = .002$; Figure 2A). The median PFS for the anlotinib group was 5.4 months (95% CI, 4.4-5.6), which was also substantially longer than the median PFS for the placebo group (1.4 months [95% CI, 1.1-1.5]; HR, 0.25 [95% CI, 0.19-0.31]; $P < .001$; Figure 2B).

Figure 2. Kaplan-Meier Estimates of Overall and Progression-Free Survival



A, For the anlotinib group, the median overall survival (OS) was 9.6 months (95% CI, 8.2-10.6); for the placebo group, the median OS was 6.3 months (95% CI, 5.0-8.1). The hazard ratio (HR) was 0.68 (95% CI, 0.54-0.87; $P = .002$).
 B, For the anlotinib group, the median progression-free survival (PFS) was 5.4 months (95% CI, 4.4-5.6). For the placebo group, the median PFS was 1.4 months (95% CI, 1.1-1.5). The HR was 0.25 (95% CI, 0.19-0.31; $P < .001$).

The OS and PFS benefits in favor of anlotinib were observed across most predefined subgroups (Figure 3; eTable 3 in Supplement 2). Patients with *EGFR* mutation had an HR of 0.59 (95% CI, 0.37-0.93) for OS and an HR of 0.15 (95% CI, 0.09-0.24) for PFS. Those without *EGFR* mutation had an HR of 0.73 (95% CI, 0.55-0.97) for OS and an HR of 0.29 (95% CI, 0.22-0.39) for PFS. In terms of the different pathological types, patients with adenocarcinoma had an HR of 0.67 (95% CI, 0.51-0.89) for OS and an HR of 0.21 (95% CI, 0.15-0.28) for PFS; both OS and PFS benefits were obtained from anlotinib. In patients with squamous cell carcinoma and other pathological types, only improved PFS was observed (HR, 0.37 [95% CI, 0.22-0.60]).

Our post hoc analysis (eTable 4 in Supplement 2) showed that, after disease progression, more patients in the placebo group compared with the anlotinib group received subsequent treatment (93 [65.0%] vs 143 [48.6%]; $P = .002$), especially chemotherapy (59 [41.3%] vs 66 [22.5%]; $P < .001$).

The objective response rate was significantly higher in the anlotinib group compared with the placebo group (27 [9.2%] vs 1 [0.7%]; $P < .001$). The difference of disease control rate

between anlotinib and placebo groups was also statistically significant (238 [81.0%] vs 53 [37.1%]; $P < .001$) (eFigure 1 in Supplement 2).

Changes in the QLQ-C30 and QLQ-LC13 scores in the first, second, fourth, and sixth treatment cycle from baseline are shown in eFigures 2 and 3 in Supplement 2. Mean increase in QLQ-LC13 total score was small in the anlotinib group in the first, second, and fourth treatment cycle. The QLQ-C30 analysis showed that patients in the anlotinib group maintained their major health status throughout the cycles from baseline.

The most common adverse events with statistical difference between the 2 groups were observed in the anlotinib group and included hypertension, fatigue, thyroid-stimulating hormone elevation, anorexia, hypertriglyceridemia, hand-foot syndrome, and hypercholesterolemia (eTable 5 in Supplement 2). During the treatment in the anlotinib group, 24 patients (8.2%) had their dose adjusted to 10 mg/d and 2 patients (0.7%) had their dose adjusted to 8 mg/d. The major reasons for dose reduction were hand-foot syndrome ($n = 7$) and hypertension ($n = 3$). Adverse events of grade 3 or higher were reported in 182 patients (61.9%) in the anlotinib group and 53 patients (37.1%) in the placebo group. Of these, the most common grade 3 or higher adverse events among the anlotinib group were hypertension (40 [13.6%]), hyponatremia (24 [8.2%]), and elevated γ -glutamyltransferase (16 [5.4%]). Twenty patients (6.8%) in the anlotinib group and 8 patients (5.6%) in the placebo group died during the 30-day follow-up period after the last dose of the study treatment was administered, and no death was found to be associated with anlotinib.

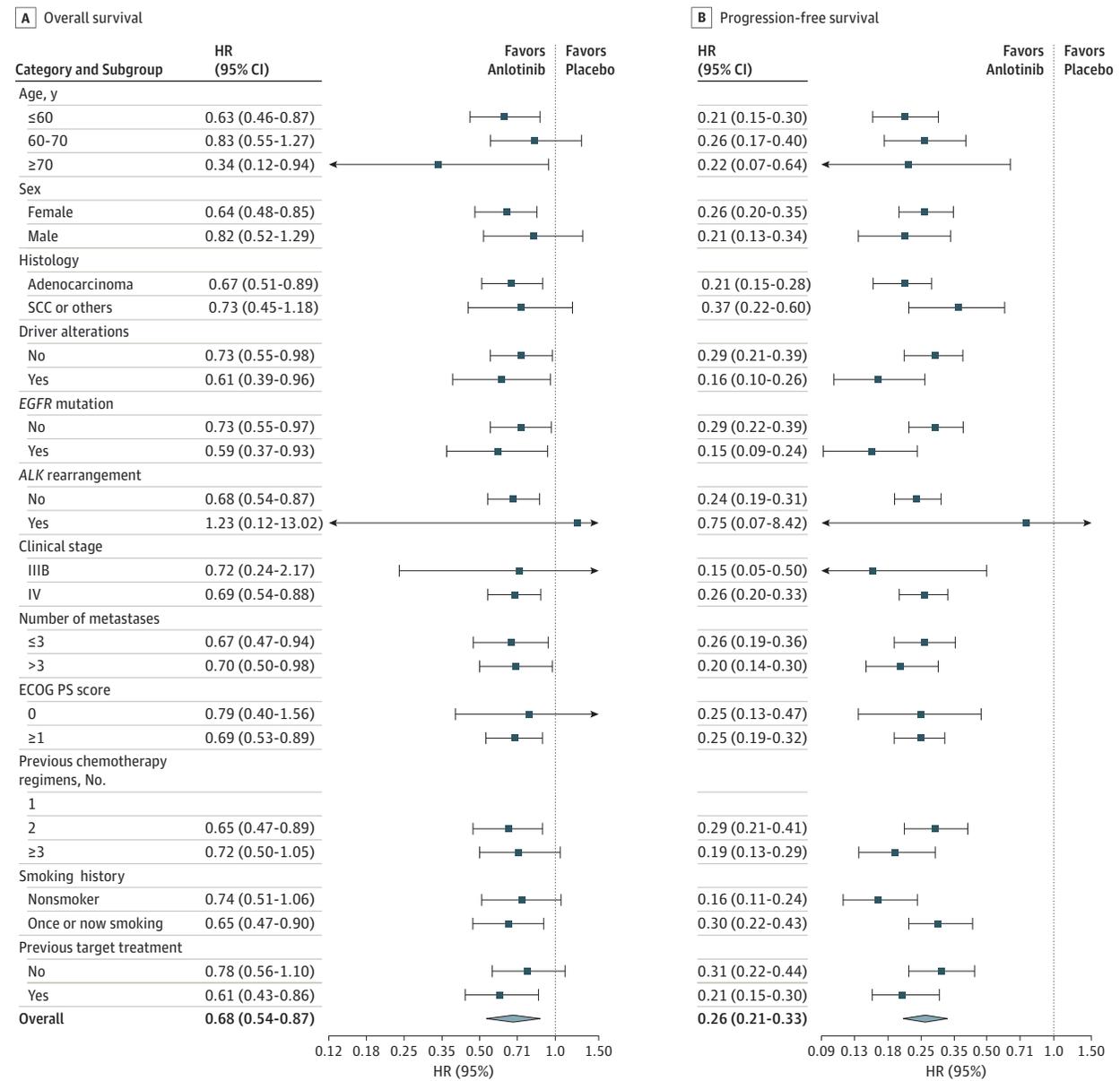
Discussion

This trial met its primary end point on the last day of data cut-off. The results showed that patients with advanced NSCLC who received anlotinib as third-line or further therapy had better OS, PFS, and objective response rate compared with patients who received placebo pills. Anlotinib was well tolerated, and the patient-reported outcome analysis revealed that patients in the anlotinib group generally maintained a reasonable quality of life.

To our knowledge, the present study is the first phase 3 trial in the third-line or beyond setting that compared a multitarget agent with placebo to show an OS benefit. In phase 2 of this trial, prolongation of PFS was achieved; however, OS was not significant between the anlotinib and placebo arms, which contrasts with the results in phase 3.¹⁰ This discrepancy may be explained by the small sample size in the phase 2 trial—only 117 patients were enrolled. In the phase 2 trial, close attention was not directed toward patients' driver alterations, as *EGFR* status was unknown in 60.7% of the total population. Considering the effect on OS of driver alterations and the corresponding targeted therapies as subsequent therapy, all patients in the phase 3 study provided specimens before enrollment to detect these driver alterations.

The number of previous targeted treatment regimens, *EGFR* mutation, and *ALK* rearrangement was balanced across the 2 arms. In addition, the proportion of patients in the anlotinib

Figure 3. Subgroup Analysis of Overall and Progression-Free Survival



ECOG PS indicates Eastern Cooperative Oncology Group Performance Status (score range: 0-5, with the highest score indicating death); EGFR, endothelial growth factor receptor; HR, hazard ratio; and SCC, squamous cell carcinoma.

group who received subsequent therapies was not larger than that in the placebo group, suggesting that the recorded OS benefit was attributable to anlotinib but not to either subsequent targeted treatment or other therapies. After data cutoff (January 6, 2017), we continued the OS follow-up until May 18, 2017. Further survival analysis showed a median OS of 9.6 months for the anlotinib group, which was 3.3 months longer than that for the placebo group. Second-line docetaxel has been shown to improve survival in NSCLC by a median of 3 months.¹³ However, few trials have focused on evaluating docetaxel as the third-line or further therapy, and retrospective evidence only shows an objective response rate of 2.3%.¹⁴ Recently, a meta-

analysis confirmed that immune checkpoint inhibitors compared with docetaxel could substantially improve OS in NSCLC as a second-line therapy; the median OS of immune checkpoint inhibitors ranged from 9.2 to 13.8 months.¹⁵ As for the third-line or further setting, the ATLANTIC study (A Global Study to Assess the Effects of MEDI4736 [Durvalumab] in Patients With Locally Advanced or Metastatic Non Small Cell Lung Cancer) has evaluated durvalumab as a third-line or later treatment in advanced NSCLC, and the median OS from this drug ranged from 9.3 to 13.3 months in different cohorts.¹⁶

As a multiple target TKI, the target molecules of anlotinib include vascular endothelial growth factor receptor 1 to 3, EGFR,

platelet-derived growth factor receptor α and β , fibroblast growth factor receptor 1 to 3, and stem cell factor receptor,⁷⁻⁹ all of which contribute to inhibitory action on tumor angiogenesis and partial tumor cell growth function. During the treatment, only 24 (8.2%) patients reduced their dose to 10 mg/d and 2 (0.7%) patients' dose was decreased to 8 mg/d, which indicates that anlotinib was well tolerated by patients with limited toxicity. The tolerable profile of anlotinib results from the treatment schedule of 2 weeks on-treatment followed by 1 week off-treatment; the low dose of the drug, which is related to a low IC_{50} concentration⁸; the rapid absorption through the intestine; a long half-life of 116 (± 47) hours; a T_{max} of 7.3 (± 3.3) hours; and the stable plasma concentration within the treatment window. High frequency of grade 3 toxicity at 10 mg/d for 4 consecutive weeks was observed in phase 1 of the trial.⁷ Therefore, high oral bioavailability and adherence may be a few of the reasons for the increased survival outcomes.

In the present study, subgroup analysis showed that the improvement in PFS and OS for patients with NSCLC was consistent with most analyzed subgroups. For example, anlotinib was found to be effective in PFS and OS for patients in both *EGFR*-mutated and *EGFR* wild-type subgroups (eFigure 5 in Supplement 2). By contrast, other multitargeted agents, such as sorafenib (Monotherapy Administration of Sorafenib in Patients With Non-Small Cell Lung Cancer [MISSION] trial), were reported to be more effective in patients with *EGFR* mutation.¹⁷ One potential reason for this difference might be that the improvement in OS among patients with *EGFR* mutation could be partly biased by the unbalanced use of *EGFR* TKIs between the sorafenib arm (19 [43.2%] patients) and the placebo arm (8 [17.7%] patients) during the subsequent treatments.¹⁸ For squamous lung cancer, previous discoveries have established that the fibroblast growth factor signaling pathway plays a fundamental role in cancer development by supporting tumor angiogenesis and cancer cell proliferation via different mechanisms.¹⁹⁻²¹ However, in previous trials, multiple target receptor TKIs, such as vandetanib, did not show efficacy in this population, although it is against fibroblast growth factor receptor.²² In the current study, considerable OS improvement was not seen in patients with squamous cell carcinoma either (HR, 0.73 [95% CI, 0.45-1.18]; $P = .19$), but a substantially improved PFS was achieved in this population. Because the squamous cell carcinoma subgroup included only 101

patients, further analysis of the efficacy of anlotinib in this population is planned.

The most common adverse events from the use of other TKIs—such as gefitinib, erlotinib hydrochloride, and afatinib dimaleate, which are used in first-line treatment of *EGFR*-mutated advanced NSCLC—are gastrointestinal (diarrhea and stomatitis/mucositis) and cutaneous (erythra, dry skin, and paronychia) conditions.²³ However, one of the main concerns with any antiangiogenic treatment is bleeding, as has occurred with bevacizumab, a humanized antibody against vascular endothelial growth factor, that has caused adverse events such as hypertension, proteinuria, bleeding, and thrombosis.²⁴ In this trial, a similar level of adverse events was observed, but the occurrence of bleeding events was low.

Limitations

This trial has some limitations. First, at the start of this trial, third-line therapy options for patients with NSCLC were nonexistent, saying nothing of any recommended salvage regimens approved in China; thus, we chose placebo as the control. A dramatic change has taken place in the past 2 years. The development of immune checkpoint inhibitors has placed docetaxel or checkpoint inhibitor as a third-line therapy for NSCLC. The PFS of third-line or further anlotinib in the present study seems to be not inferior to the results achieved by docetaxel or nivolumab in previous reports. Head-to-head comparisons of anlotinib and chemotherapy as third-line treatment are beneficial to identify the sequence of therapy strategies. Second, potential biomarkers were not reported in this study. The analysis of biomarkers, such as C-C motif ligand 2 and active circulating endothelial cells, suitable for anlotinib therapy using tissue or cancerous pleural effusion specimens is still ongoing. These results will be reported in the future.

Conclusions

Anlotinib as third-line and further therapy is well tolerated and offers significantly improved PFS and OS compared with placebo among Chinese patients in our trial. Anlotinib is a potential treatment option for the management of patients with advanced NSCLC. Future studies will look into the therapeutic strategies for anlotinib combined or compared with other therapies in NSCLC and other solid tumors.

ARTICLE INFORMATION

Accepted for Publication: May 8, 2018.

Published Online: August 9, 2018.

doi:10.1001/jamaoncol.2018.3039

Open Access: This article is published under the *JN-OA license* and is free to read on the day of publication.

Author Affiliations: Department of Pulmonary Medicine, Shanghai Chest Hospital, Shanghai Jiaotong University, Shanghai, China (Han, Yizhuo Zhao); Department of Thoracic Oncology, Tianjin Medical University Cancer Hospital, Tianjin, China (K. Li); Department of Internal Medicine, Affiliated Cancer Hospital of Zhengzhou University,

Zhengzhou, China (Q. Wang); Henan Cancer Hospital, Zhengzhou, China (Q. Wang); Department of Respiratory Diseases, Peking Union Medical College Hospital, Beijing, China (Zhang); Department of Oncology, Linyi Cancer Hospital, Linyi, China (J. Shi); Department of Internal Medicine-Oncology, Shandong Cancer Hospital, Jinan, China (Z. Wang); Department of Thoracic Oncology, Jilin Cancer Hospital, Changchun, China (Cheng); Department of Thoracic Surgery, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China (He); Department of Medical Oncology, Cancer Hospital Chinese Academy of Medical Sciences, Beijing, China (Y. Shi, Sun); Department of Biostatistics, School of Public

Health, Nanjing Medical University, Nanjing, China (Yu, Yang Zhao); Department of Pulmonary Medicine, Lanzhou Military General Hospital, Lanzhou, China (Chen); Department of Medical Oncology, Hunan Cancer Hospital, Changsha, China (Luo, Wu); Department of Chemotherapy, Qilu Hospital of Shandong University, Jinan, China (X. Wang); Department of Medicine I, Medical University of Vienna, Vienna, Austria (Pirker); Department of Oncology, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China (Nan); Department of Respiratory Diseases, Tang Du Hospital, Xi'an, China (Jin); First Department of Medical Oncology, Yunnan Cancer Hospital, Kunming, China (Dong); Department of General

Medicine, Capital Medical University, Beijing Chest Hospital, Beijing, China (B. Li).

Author Contributions: Drs Han and K. Li had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Han and K. Li contributed equally to this work.

Study concept and design: Han, K. Li, Q. Wang, Zhang, Z. Wang, Cheng, He, Yizhuo Zhao, Chen, Wu, X. Wang, Nan, Jin, Dong, B. Li, Sun.

Acquisition, analysis, or interpretation of data: Han, K. Li, Q. Wang, Zhang, J. Shi, Z. Wang, He, Y. Shi, Yizhuo Zhao, Yu, Yang Zhao, Chen, Luo, Wu, X. Wang, Pirker, Nan, Jin, Dong, B. Li.

Drafting of the manuscript: Han, K. Li, Q. Wang, Zhang, Z. Wang, He, Yizhuo Zhao, Yang Zhao, Chen, Wu, X. Wang, Pirker, Nan, Jin, Dong, B. Li.

Critical revision of the manuscript for important intellectual content: Han, K. Li, J. Shi, Cheng, He, Y. Shi, Yu, Yang Zhao, Luo, Pirker, Dong, Sun.

Statistical analysis: Han, J. Shi, He, Yu, Yang Zhao.

Obtained funding: Han.
Administrative, technical, or material support: Han, K. Li, Q. Wang, Zhang, Z. Wang, He, Yizhuo Zhao, Chen, Luo, Wu, X. Wang, Nan, Jin, Dong, B. Li, Sun.
Study supervision: Han, K. Li, He, Chen.

Conflict of Interest Disclosures: Dr Han reported consulting for AstraZeneca and Roche Pharmaceutical Company as well as receiving speaking fees from AstraZeneca Pharmaceutical Company and Lilly Pharmaceutical Company. No other disclosures were reported.

Funding/Support: This study was supported by Chia Tai Tianqing Pharmaceutical Group Co, Ltd.

Role of the Funder/Sponsor: The funding source had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. The funder collaborated with the investigators in designing the trial, provided the study drug, and coordinated the management of the study sites.

Meeting Presentation: The preliminary results of this study were presented at the American Society of Clinical Oncology Annual Meeting; June 3, 2017; Chicago, Illinois.

Additional Contributions: We thank the patients and their families as well as the investigators and study teams for their participation in the study. We also thank the Independent Data Monitoring committee (led by Dr Zhang) and the following people for their valuable review comments: Shirish Madhav Gadgil, MD, Wayne State University/Karmanos Cancer Institute; Gregory P. Kalemkerian, MD, University of Michigan Medical School, Ann Arbor; Matthew Evison, MD, University Hospital of South Manchester; Charles B. Simone, MD, University of Maryland Medical Center; Shinji Sasada, MD, PhD, National Cancer Center Hospital; Federico Cappuzzo, MD, AUSL della Romagna; Filippo De Marinis, MD, Gianluca Spitaleri, MD, and Stefania Rizzo, MD, PhD, European Institute of Oncology; Susumu S. Kobayashi, MD, PhD, Beth Israel Deaconess Medical Center; Nobuhiko Seki, MD, Teikyo University School of Medicine; Luca Bertolaccini, MD, PhD, Maggiore Teaching Hospital; Sai-Hong Ignatius Ou, MD, PhD, University of California Irvine School of Medicine; Percy Lee, MD, UCLA (University of California, Los Angeles); Ross

A. Soo, MD, National University Health System; Patrick C. Ma, MD, West Virginia University; and Xiuning Le, MD, PhD, Beth Israel Deaconess Medical Center, Harvard Medical School.

REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer*. 2015;136(5):E359-E386. doi:10.1002/ijc.29210
2. Chen W, Zheng R, Baade PD, et al. Cancer statistics in China, 2015. *CA Cancer J Clin*. 2016;66(2):115-132. doi:10.3322/caac.21338
3. Miller KD, Siegel RL, Lin CC, et al. Cancer treatment and survivorship statistics, 2016. *CA Cancer J Clin*. 2016;66(4):271-289. doi:10.3322/caac.21349
4. Maione P, Rossi A, Sacco PC, Bareschino MA, Schettino C, Gridelli C. Advances in chemotherapy in advanced non-small-cell lung cancer. *Expert Opin Pharmacother*. 2010;11(18):2997-3007. doi:10.1517/14656566.2010.511615
5. Chan BA, Hughes BG. Targeted therapy for non-small cell lung cancer: current standards and the promise of the future. *Transl Lung Cancer Res*. 2015;4(1):36-54.
6. Jänne PA, van den Heuvel MM, Barlesi F, et al. Selumetinib Plus Docetaxel Compared With Docetaxel Alone and Progression-Free Survival in Patients With KRAS-Mutant Advanced Non-Small Cell Lung Cancer: the SELECT-1 randomized clinical trial. *JAMA*. 2017;317(18):1844-1853. doi:10.1001/jama.2017.3438
7. 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(1):105. doi:10.1186/s13045-016-0332-8
8. Lin B, Song X, Yang D, Bai D, Yao Y, Lu N. Anlotinib inhibits angiogenesis via suppressing the activation of VEGFR2, PDGFR β and FGFR1. *Gene*. 2018;654:77-86. doi:10.1016/j.gene.2018.02.026
9. Taurin S, Yang CH, Reyes M, et al. Endometrial cancers harboring mutated fibroblast growth factor receptor 2 protein are successfully treated with a new small tyrosine kinase inhibitor in an orthotopic mouse model. *Int J Gynecol Cancer*. 2018;28(1):152-160.
10. Han B, Li K, Zhao Y, et al. Anlotinib as a third-line therapy in patients with refractory advanced non-small-cell lung cancer: a multicentre, randomised phase II trial (ALTER0302). *Br J Cancer*. 2018;118(5):654-661. doi:10.1038/bjc.2017.478
11. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA*. 2013;310(20):2191-2194. doi:10.1001/jama.2013.281053.
12. Garon EB, Ciuleanu TE, Arrieta O, et al. Ramucicromab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. *Lancet*. 2014;384(9944):665-673. doi:10.1016/S0140-6736(14)60845-X
13. Shepherd FA, Dancey J, Ramlau R, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. *J Clin Oncol*. 2000;18(10):2095-2103. doi:10.1200/JCO.2000.18.10.2095
14. Massarelli E, Andre F, Liu DD, et al. A retrospective analysis of the outcome of patients who have received two prior chemotherapy regimens including platinum and docetaxel for recurrent non-small-cell lung cancer. *Lung Cancer*. 2003;39(1):55-61. doi:10.1016/S0169-5002(02)00308-2
15. Lee CK, Man J, Lord S, et al. Clinical and molecular characteristics associated with survival among patients treated with checkpoint inhibitors for advanced non-small cell lung carcinoma: a systematic review and meta-analysis. *JAMA Oncol*. 2018;4(2):210-216. doi:10.1001/jamaoncol.2017.4427
16. Garassino MC, Cho BC, Kim JH, et al; ATLANTIC Investigators. Durvalumab as third-line or later treatment for advanced non-small-cell lung cancer (ATLANTIC): an open-label, single-arm, phase 2 study. *Lancet Oncol*. 2018;19(4):521-536. doi:10.1016/S1470-2045(18)30144-X
17. Paz-Ares L, Hirsh V, Zhang L, et al. Monotherapy Administration of Sorafenib in Patients With Non-Small Cell Lung Cancer (MISSION) trial: a phase III, multicenter, placebo-controlled trial of sorafenib in patients with relapsed or refractory predominantly nonsquamous non-small-cell lung cancer after 2 or 3 previous treatment regimens. *J Thorac Oncol*. 2015;10(12):1745-1753.
18. Mok TS, Paz-Ares L, Wu YL, et al. Association between tumor EGFR and KRAS mutation status and clinical outcomes in NSCLC patients randomized to sorafenib plus best supportive care (BSC) or BSC alone: subanalysis of the phase III MISSION trial. *Ann Oncol*. 2012;23(suppl 9):ixel. doi:10.1093/annonc/mds499
19. Tiseo M, Gelsomino F, Alfieri R, et al. FGFR as potential target in the treatment of squamous non small cell lung cancer. *Cancer Treat Rev*. 2015;41(6):527-539. doi:10.1016/j.ctrv.2015.04.011
20. Helsten T, Schwaederle M, Kurzrock R. Fibroblast growth factor receptor signaling in hereditary and neoplastic disease: biologic and clinical implications. *Cancer Metastasis Rev*. 2015;34(3):479-496. doi:10.1007/s10555-015-9579-8
21. Procopio MG, Laszlo C, Al Labban D, et al. Combined CSL and p53 downregulation promotes cancer-associated fibroblast activation. *Nat Cell Biol*. 2015;17(9):1193-1204. doi:10.1038/ncb3228
22. Heymach JV, Paz-Ares L, De Braud F, et al. Randomized phase II study of vandetanib alone or with paclitaxel and carboplatin as first-line treatment for advanced non-small-cell lung cancer. *J Clin Oncol*. 2008;26(33):5407-5415. doi:10.1200/JCO.2008.17.3138
23. Califano R, Tariq N, Compton S, et al. Expert consensus on the management of adverse events from EGFR tyrosine kinase inhibitors in the UK. *Drugs*. 2015;75(12):1335-1348. doi:10.1007/s40265-015-0434-6
24. Boehm S, Rothermundt C, Hess D, Joerger M. Antiangiogenic drugs in oncology: a focus on drug safety and the elderly—a mini-review. *Gerontology*. 2010;56(3):303-309. doi:10.1159/000262450