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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

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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 0303 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 cavitary 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; = .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]; < .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.

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Supplemental content

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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.

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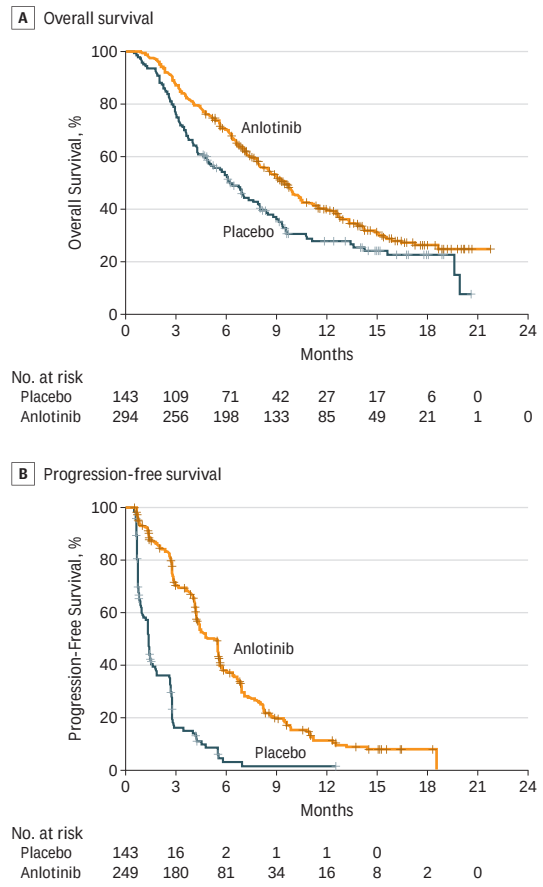
Figure 2. Kaplan-Meier Estimates of Overall and Progression-Free Survival



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; = .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; < .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 OLQ-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 cutoff. 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

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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.

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} concentration[8]; 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.

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