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Supplemental Appendix for:
The Impact of Anlotinib on Brain Metastases of NSCLC: Post-hoc Analysis of a Phase III Randomized Control Trial (ALTER0303)
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Supplementary: methods

Study design and patients

All data were retrieved from the ALTER trial (a multicenter, double-blind, randomized phase 3 clinical trial (ALTER trial: NCT02388919)) 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. All patients provided written informed consent before entering the trial. Details on patient eligibility criteria, stratification, and randomization between study treatment arms were described previously [1].

Treatment and assessments

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 chemotherapy and TKI therapy for all patients with driver alterations mutation or ALK 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 cavitary features or brain metastases that were uncontrolled or controlled for less than 2months.

Patients were randomized to receive anlotinib or placebo in a 2-to-1-ratio. The medication was administered from days 1 to 14 in a 21-day cycle, and the initial dose of oral anlotinib was (12 mg/d). 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. 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. If the patient had BM at baseline, brain MRI was examined every cycle. If the patient did not have BM at baseline, brain MRI examination would be performed in case of the patient was suspected with brain metastasis or clinical symptoms.

Outcomes

OS was defined as the duration between randomization and death from any cause. For patients who were considered lost to follow-up, the date of the last follow-up visit was calculated equally as the date of death. PFS was defined as the duration between randomization and objective tumor progression or death. Time to brain progression (TTBP) as the duration between randomization and objective intracranial progression. 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

Demographic and baseline characteristics were presented as categorical variables. Comparisons between categorical variables were performed using Pearson Chi-square test or Fisher's exact test, as appropriate. The between-group comparisons of PFS, OS and TTBP were performed by multivariate Cox proportional hazards models. Subgroup analyses in TTBP were assessed with the use of stratified Cox proportional-hazards model by

randomized stratification factors. All statistical tests were two-sided and all tests were considered significant for P values below 0.05. Statistical analysis was performed using SPSS statistics version 25.0 (IBM Corp, Armonk, NY).

Reference:

1. Han B, Li K, Wang Q, Zhang L, Shi J, Wang Z, Cheng Y, He J, Shi Y, Zhao Y *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**(11):1569-1575.