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Quality of life results from a randomized, double-blinded, placebo-controlled, multi-center phase III trial of anlotinib in patients with advanced non-small cell lung cancer

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ABSTRACT

Objectives: Anlotinib is a novel multi-target tyrosine Kinase inhibitor that inhibits VEGFR2/3, FGFR1-4, PDGFD α/β, c-Kit and Ret. In the phase III ALTER-0303 trial (Clinical Trial Registry ID: NCT 02388919), anlotinib significantly improved overall survival versus placebo in advanced non-small-cell lung cancer (NSCLC) patients who had received at least two previous chemotherapy and epidermal growth factor receptor/anaplastic lymphoma kinase targeted therapy regimens. This study assessed quality of life (QoL) in these patients.

Methods: Patients were randomized (2:1) to anlotinib or placebo up to progression or intolerable toxicity. The QoL were assessed using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) and the associated EORTC Quality of Life Lung Cancer Specific Module (QLQ-LC13) at baseline, end of cycle 1, end of every two cycles, and at the final visit. The analyses were conducted in the first 6 cycles. Differences in scores of 10 points or more between two arms or from baseline were considered clinically meaningful.

Results: A total of 437 patients were assigned to anlotinib (n = 294) and placebo (n = 143). The completion rates of the QoL questionnaires were from 69.9% to 97.0%. Mean scores of QLQ-C30 and QLQ-LC13 subscales were similar in the anlotinib and placebo arms at baseline. Compared to placebo, anlotinib improved role functioning, social functioning, dyspnea, insomnia, constipation and financial problems. Only sore mouth or tongue symptom was worse in the anlotinib arm than in the placebo arm.

Conclusions: Anlotinib improved quality of life versus placebo in advanced NSCLC patients who had received at

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least two previous chemotherapies. The QoL analyses provided evidence that anlotinib should be a choice for the third-line treatment or beyond in advanced NSCLC.

1. Introduction

Lung cancer is the leading incident cancer and cause of cancer mortality worldwide [1]. More than 80% of lung cancers are non-small cell lung cancer (NSCLC). There are no standard-of-care third-line treatment for advanced NSCLC patients who had failed with two previous chemotherapy and epidermal growth factor receptor(EGFR)/anaplastic lymphoma kinase (ALK) targeted therapy regimens.

Anlotinib is a novel multi-target tyrosine Kinase inhibitor that inhibits VEGFR2/3, FGFR1-4, PDGFD α/β, c-Kit and Ret. At the dose of 12 mg once daily at the 2/1 schedule, anlotinib displayed manageable toxicity and antitumor potential [2]. The ALTER-0303 trial (NCT02388919) showed anlotinib significantly improved overall survival in advanced NSCLC with manageable safety profile [3]. The results strongly suggest that anlotinib should be considered as a candidate for the third-line treatment or beyond in advanced NSCLC.

The effects of treatment on the palliation of symptoms and improvement or maintenance of quality of life (QoL) are important considerations in the choice of therapy. Few studies have reported on quality of life in the third-line treatment of NSCLC.

In ALTER-0303, the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) and the associated EORTC Quality of Life Lung Cancer Specific Module (QLQ-LC13) were used to analyze quality of life.

2. Patients and methods

2.1. Study design

The full details of the study design have been previously published [4]. The study was a multicenter, double-blinded, randomized phase III trial comparing anlotinib and placebo in advanced NSCLC patients who had received at least two previous chemotherapy and EGFR/ALK targeted therapy regimens. The study was conducted at 31 centers in China. Pathological stage IIIB/IV advanced NSCLC patients who had failed with at least two previous chemotherapy and EGFR/ALK targeted therapy regimens were eligible. The status of EGFR and ALK genes should be clear in all enrolled patients. Patients with sensitive EGFR or ALK mutations must had received and appeared intolerance to previous targeted therapies. Patients were randomized (2:1) to receive anlotinib or placebo once daily (12 mg) from day 1–14 of a 21-day cycle until progression or intolerable toxicity. Dose reduction to 8 or 10 mg daily could be applied when grade 3 or 4 treatment-related toxicities were observed. The ethics review board at each site approved the study protocol, and the study was conducted in accordance with the Good Clinical Practice guidelines and the Declaration of Helsinki. All patients provided written informed consent before undergoing any study procedure. The study was registered at the ClinicalTrials.gov website (ClinicalTrials.gov identifier, NCT 02388919).

2.2. QoL assessments

QoL was assessed using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) and the associated EORTC Quality of Life Lung Cancer Specific Module (QLQ-LC13) [5,6]. The QLQ-C30, a 30-item questionnaire, included five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, nausea, and vomiting), and one global health and QoL scales. The QLQ-LC13 comprises 13 items that assess lung cancer related symptoms (cough, hemoptysis, and dyspnea) and treatment related side-effects (sore mouth or tongue, dysphagia, hair loss, tingling hands and feet, pain, and pain medication). All items are rated on a 4-point scale and 7-point numerical analog scale with a reporting time of 1 week. The measurements were collected at baseline, end of cycle 1, end of every two cycles, and at the final visit.

2.3. Statistical analysis

The QLQ-C30 and QLQ-LC13 analyses were conducted on the full analysis set (FAS) population. The FAS population included all randomized patients in the groups. QLQ-C30 and QLQ-LC13 subscale scores were compared between the anlotinib and placebo arms, and change from the baseline. For each scale or item, a linear transformation was applied to standardize the raw score to a range of 0–100. Differences in any scores of ≥10 points were considered clinically meaningful, and was used to classified as improved (≥10-point increase for functioning scales; ≥10-point decrease for symptom scales/items), stable, or wor-

Table 1
Patient Demographics and Baseline Disease Characteristics.

characteristics	Placebo (n = 143)	Anlotinib (n = 294)	
Gender, No. (%)			
Male	97(67.8)	188(63.9)	P = .455
Age (years)			
Mean	56.8	57.9	P = .207
Range	31.00 – 74.00	20.00 – 75.00	
Histology, No. (%)			P = .145
Adenocarcinoma	108(75.52)	228(77.55)	
Squamous cell or adenosquamous carcinoma	33(23.08)	53(18.03)	
others	2(1.40)	13(4.42)	
Stage No. (%)			P = 1.000
IIIB	7(4.90)	15(5.10)	
IV	136(95.10)	277(94.22)	
EGFR mutation	45(31.47)	93(31.63%)	P = 1.000
ALK rearrangement	2(1.41)	5(1.72%)	P = 1.000
ECOG PS			P = .246
0	22(15.38)	59(20.07)	
1	120(83.92)	233(79.25)	
2	1(0.70)	2(0.68)	

EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; ECOG PS, Eastern Cooperative Oncology Group performance status.

Table 2
Compliance with Quality of Life Questionnaires.

	Placebo Arm		Anlotinib Arm	
	Patients on study, No.	Completed, No. (%)*	Patients on study, No.	Completed No. (%)*
baseline	143	132 (92.3)	294	279 (94.9)
End of Cycle 1	143	100 (69.9)	294	230 (78.2)
End of Cycle 2	81	71 (87.6)	266	239 (89.8)
End of Cycle 4	39	33 (84.6)	218	204 (93.6)
End of Cycle 6	15	13 (86.7)	168	163 (97.0)

* Based on the number of on-study patients in the arm.