Original Article

Equivalent efficacy assessment of QL1101 and bevacizumab in nonsquamous non-small cell lung cancer patients: A two-year follow-up data update

Jun Lu[1,2,3,4*], Tianqing Chu[1*], Hongyu Liu[1*], Minjuan Hu[1], Yuqing Lou[1], Yanwei Zhang[1], Zhiqiang Gao[1], Wei Zhang[1], Xueyan Zhang[1], Huimin Wang[1], Hua Zhong[1], Baohui Han[1,2,3]

[1]Department of Pulmonary Medicine, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai 200030, China; [2]Shanghai Institute of Thoracic Oncology, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai 200030, China; [3]Translational Medical Research Platform for Thoracic Oncology, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai 200030, China; [4]Department of Bio-bank, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai 200030, China

*These authors contributed equally to this work.

Correspondence to: Baohui Han, PhD. Department of Pulmonary Medicine, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai 200030, China. Email: 18930858216@163.com; Hua Zhong, PhD. Department of Pulmonary Medicine, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai 200030, China. Email: eddiedong8@hotmail.com.

Abstract

Objective: Anti-vascular endothelial growth factor (VEGF) monoclonal antibodies are an effective means of treating non-small cell lung cancer (NSCLC). Here, we aim to update the equivalent efficacy assessment between QL1101 and bevacizumab based on two-year follow-up data.

Methods: In total, 535 eligible NSCLC patients were enrolled in this randomized controlled trial. Patients were randomly assigned 1:1 to the QL1101 group and the bevacizumab group. The full end time of this study was defined as 24 months after the last enrolled patient was randomized. The primary endpoint was the objective response rate (ORR); equivalence was confirmed if the two-sided 90% confidence interval (90% CI) of the relative risk was within the range of 0.75−1.33. The secondary endpoints were progression-free survival (PFS) and overall survival (OS).

Results: The two-year updated data showed similar ORR (QL1101 *vs.* bevacizumab: 53.1% *vs.* 54.3%; relative risk=0.977; 90% CI: 0.838−1.144), PFS (235 d *vs.* 254 d, log-rank P=0.311), and OS (577 d *vs.* 641 d, log-rank P=0.099) results between the QL1101 group and the bevacizumab group. The mean shrinkage ratio of targeted lesions was also similar between the QL1101 group and the bevacizumab group (22.5% *vs.* 23.5%). For patients who received QL1101 maintenance therapy, similar results were shown between the QL1101 group (n=157) and the bevacizumab group (n=148) (PFS: 253 d *vs.* 272 d, log-rank P=0.387; OS: 673 d *vs.* 790 d, log-rank P=0.101; mean tumor shrinkage rate: 26.6% *vs.* 27.5%).

Conclusions: This study reported that QL1101 had similar efficacy in treating nonsquamous NSCLC in terms of ORR, PFS and OS based on two-year updated data, providing a basis for the clinical application of QL1101.

Keywords: QL1101; biosimilar; non-small cell lung cancer; bevacizumab; VEGF

Submitted Nov 02, 2021. Accepted for publication Dec 31, 2021.
doi: 10.21147/j.issn.1000-9604.2022.01.03
View this article at: https://doi.org/10.21147/j.issn.1000-9604.2022.01.03

Introduction

Non-small cell lung cancer (NSCLC) accounts for approximately 85% of lung cancer and is one of the leading causes of cancer-related death (1-4). Chemotherapy has played a cornerstone role in the history of NSCLC therapy

since the 20th century (5-7). In 2006, a novel monoclonal antibody (bevacizumab) against vascular endothelial growth factor (VEGF) was discovered to inhibit NSCLC development in a clinical trial (8). Interestingly, monotherapy with bevacizumab did not significantly prolong the progression-free survival (PFS) and overall survival (OS) of NSCLC patients, whereas combined therapy with bevacizumab and chemotherapy remarkably prolonged PFS and OS (8). This study established the roles of antiangiogenic bevacizumab in combination with chemotherapy for NSCLC in clinical practice. This treatment regimen remains one of the primary therapies recommended by National Comprehensive Cancer Network (NCCN) guidelines for patients with nonsquamous NSCLC without specific driver gene mutations (*EGFR*, *ALK* and *ROS1*) (7).

Due to the complex signaling pathways of antiangiogenic targets, there were no advances in the development of new antiangiogenic agents approximately 10 years after bevacizumab was approved for NSCLC clinical practice (2,6,9,10). To date, bevacizumab, an outstanding representative antiangiogenic agent, has been used to prolong the survival time of NSCLC in clinical practice (7). However, the availability of bevacizumab limits the balance between controlling the cost and improving access (6,11-14). Therefore, bevacizumab biosimilars [including QL1101 (6), ABP215 (15,16) and PF-06439535 (17)] have been developed and approved in clinical practice. QL1101, as the second bevacizumab biosimilar, was approved by the China National Medical Products Administration (NMPA) in 2019 (6).

Our previous study reported 12-month follow-up data, and the results demonstrated equivalent efficacy between bevacizumab and QL1101 (6). However, the 24-month follow-up data remain to be analyzed. In the present study, we further report the equivalent efficacy between bevacizumab and QL1101 during the 24-month follow-up.

Materials and methods

Study design

This study was a two-year follow-up data update of a multicenter, randomized, double-blind, parallel, phase III clinical trial (ClinicalTrials.gov identifier: NCT03169335). The purpose of this study was to evaluate the therapeutic equivalence between bevacizumab and QL1101 in stage IIIb or IV nonsquamous NSCLC patients in China. This study was approved by the Institutional Review Board, Ethics Committee or Organizations of Shanghai Chest Hospital (Ethics No. LS1652). The protocol design follows the Declaration of Helsinki, Drug Administration Law of the People's Republic of China, Drug Registration Regulation and Good Clinical Practice.

Inclusion and exclusion criteria

The detailed screening procedures were introduced in the protocol of QL1101. In brief, NSCLC patients that met the following criteria were included in this clinical trial: 1) age: ≥18 years and ≤75 years; 2) stage: IIIb or IV nonsquamous NSCLC; 3) Eastern Cooperative Oncology Group (ECOG) score: 0−1; 4) at least one lesion evaluated by Response Evaluation Criteria Solid Tumors (RECIST) Version 1.1; 5) patients did not receive systemic antitumor therapy; 6) expected survival time: ≥24 months; and 7) hematological parameters, liver indices, kidney indices, and heart indices met the corresponding conditions according to the protocol. NSCLC patients were excluded according to the following criteria: 1) central type of lung squamous carcinoma (LUSC) and mixed adenosquamous carcinoma; 2) patients harboring *ALK* fusion gene; 3) patients with a history of thrombotic disease in the past 6 months; 4) patients with tumor invasion into the main vessels or metastases to the central nervous system; 5) patients who received palliative radiotherapy in the past 2 weeks or underwent major surgical procedures in the past 4 weeks or minor surgical procedures within 48 h; or 6) patients with a history of hereditary bleeding tendency or uncontrolled hypertension or significant vascular diseases.

Sample size calculation

This clinical trial planned to enroll 512 subjects with nonsquamous NSCLC in line with the inclusion and exclusion criteria. Primary indicators were assessed by using the objective response rate (ORR) and 90% confidence interval (90% CI). According to 80% power, α was set to 0.1 (two-sided), the equivalence dividing value of the ORR ratio was assumed to be 0.75−1.33, and the ORR in the control group was assumed to be 50%; then, the sample size in each group was 213 patients. With a dropout rate of 20% considered, the total sample size was 512 patients.

Blinding and drug administration

In total, 675 patients participated in the screening stage, and 535 patients were enrolled in this clinical trial. The

patients were randomly assigned 1:1 to receive QL1101-based or bevacizumab-based treatment protocols with a block randomization scheme using a double-blind, computerized, randomized list generator. Briefly, subjects will be randomized to QL1101 group or bevacizumab group in a double-blind fashion so that neither the Investigator, Sponsor's study management team, clinical staff, nor the subject will know which agent is being administered. The randomization factors included age (<65 years or ≥65 years), gender (male or female), smoking history (yes or no), pathology (wild type or *EGFR* mutation), and ECOG (0 or 1). The randomization number will be assigned based on information obtained from the Interative Response Technology (IRT). QL1101 and bevacizumab (supplied by Qilu Pharmaceutical Group Co., Ltd.) will be indistinguishable from one another in appearance, and packaging for each treatment group will also be indistinguishable from one another in appearance. Patients were randomized to receive paclitaxel (175 mg/m^2 Q21d IV) plus carboplatin [area under the curve (AUC) 6 Q21 IV] in combination with either QL1101 (15 mg/kg Q21d IV) or bevacizumab (15 mg/kg Q21d IV) for 4–6 cycles followed by maintenance therapy with QL1101 (15 mg/kg Q21d IV). Because the drugs were purchased in different batches, drug blinding was conducted throughout the clinical trial.

Performance

The experimental group was treated with QL1101, paclitaxel and carboplatin, while the control group was treated with bevacizumab, paclitaxel and carboplatin. The difference between the actual dose of QL1101/bevacizumab, paclitaxel and carboplatin and the theoretical dose should not exceed ±5%. Once the combined chemotherapy treatment was completed (4–6 cycles), subjects who had no progressive disease (PD) continued to receive 15 mg/kg QL1101 for one 3-week treatment cycle until death, loss to follow-up, intolerable toxicity, end of the study, use of other antitumor prescription drugs, or withdrawal from the study. The full end time of this study was defined as 24 months after the last enrolled patient was randomized. Patients were expected to return to the study center for a final tumor evaluation 21 days (±7 days) from this point if they had not experienced PD. The study had a 28-day screening phase, and qualified patients began treatment with the study drug on the first day of the first treatment cycle. During the study phase, the investigator evaluated the efficacy and safety of QL1101/bevacizumab in accordance with the protocols of this study.

Outcomes

The primary endpoint was ORR of the two treatment groups (QL1101 *vs.* bevacizumab), which was evaluated by independent review committees (ICRs). The ORR [including complete response (CR) and partial response (PR)] was determined according to RECIST Version 1.1 at 18 weeks after treatment administration.

The secondary endpoints were the duration of response (DOR), PFS and OS at 3 months, 6 months, 9 months, 12 months and 24 months. The safety endpoint was the treatment-emergent adverse events (TEAEs) between the two groups. DOR referred to the minimum time from when CR or PR was first observed to the time of PD or death for patients whose best overall response was CR or PR. Data from the first dose to the 6th cycle (18 weeks) of treatment were compared by statistical analysis, excluding data from patients on maintenance treatment and other antitumor treatments. The duration was based on the time of the last imaging evaluation within 6 cycles. Patients without available data after the occurrence of CR or PR were recorded as censored, and the time was defined as 1 day.

PFS was defined as the time from randomization to the date of the first documented tumor progression or death from any cause, whichever occurred first. Data from the first dose to the 6th cycle (18 weeks) of treatment were compared by statistical analysis, excluding data from patients on maintenance treatment and other antitumor treatments. The duration was based on the time of the last imaging evaluation within 6 cycles. Patients without available data after dosing were recorded as censored, and the time was defined as 1 day.

OS was defined as the time from randomization to the date of death due to any cause. For patients who were lost to follow up, the date of their last contact was used as the cut-off date. Survival was defined as the date of death minus the date of randomization. The first day of the month was used as a substitute for the missing "day" on the date of death.

Analysis sets

Full analysis set (FAS): FAS was defined as all patients randomly assigned to a treatment group with least one efficacy assessment after randomization. Screened analysis set (SAS): SAS patients excluded the 84 patients who

harboring interference factors. Per protocol analysis set (PPS): PPS patients included all randomized patients who met the inclusion criteria, received at least 4 doses of QL1101/bevacizumab, completed the primary efficacy assessment, received the maintenance treatment, had good compliance, and had no serious violations of the clinical trial protocol. Safety set (SS): SS patients included all randomized patients with at least one safety assessment after randomization. Safety data were analyzed in terms of the actual treatment received. Baseline information and efficacy analysis were based on the FAS, SAS and PPS. The primary efficacy analyses were based on both SAS and PPS. Analyses of laboratory examinations, adverse events and adverse reactions were based on SS and PPS.

Statistical analysis

Statistical analyses were performed using SAS software (Version 9.3.0; SAS Institute Inc., Cary, NC, USA) and GraphPad Prism 5 (GraphPad Software, Inc., San Diego, CA, USA). The statistical description of the count data is expressed as the number of cases. For DOR equivalence analysis, multivariate analysis was performed using the Cox proportional hazards model, with randomization factors included as stratified factors for correction. A Chi-square *t* test was performed for dropout analysis to compare the total dropout rates of the two groups. The primary endpoint evaluation of ORR used the approximately Gaussian distribution method to calculate the ratio of the two groups of response rates and the corresponding 90% CI. The secondary endpoint (PFS and OS) equivalent efficacy evaluation was performed with the Kaplan-Meier method using the Mantel-Cox test [including the log-rank P values, Chi-square and 95% confidence interval (95% CI)]. The hazard ratio (HR) was obtained by Cox regression analysis. The safety equivalent evaluation was used to compare the incidence rates of adverse events (such as leukopenia, thrombocytopenia and anemia) between the two groups.

Results

Evaluation of equivalent efficacy of QL1101 and bevacizumab in terms of DOR and PFS in 535 enrolled patients

A total of 535 patients with nonsquamous NSCLC were screened for enrolment in this study. A total of 269 patients received QL1101 plus chemotherapy, and the other 266 patients received bevacizumab plus chemotherapy (*Figure 1*). For DOR equivalent evaluation, of 147 patients who received QL1101 plus chemotherapy, 120 patients had an event (censoring rate: 18.37%), with a median DOR of 187 d. Of 158 patients who received bevacizumab plus chemotherapy, 128 patients had an event (censoring rate: 18.99%), with a median DOR of 212 d. The results showed that there was no significant difference between the QL1101 group and the bevacizumab group (P=0.368) (*Figure 2A*). The HR (90% CI) for the QL1101 group compared with the bevacizumab group was 1.078 (0.870–1.337).

For the PFS equivalent evaluation, 269 patients in the QL1101 group were included in the PFS analysis, 209 of whom had an event (censoring rate: 21.43%), with a median PFS of 242 d; 266 patients in the bevacizumab group were included in the analysis, 209 of whom had an event (censoring rate: 21.43%), with a median PFS of 256 d. The HR (90% CI) of the QL1101 group and the bevacizumab group was 1.148 (0.974–1.352) (*Figure 2B*).

Equivalent efficacy analysis between QL1101 and bevacizumab in cohort of 451 patients

In our previous study (6), we reported that *EGFR* mutation

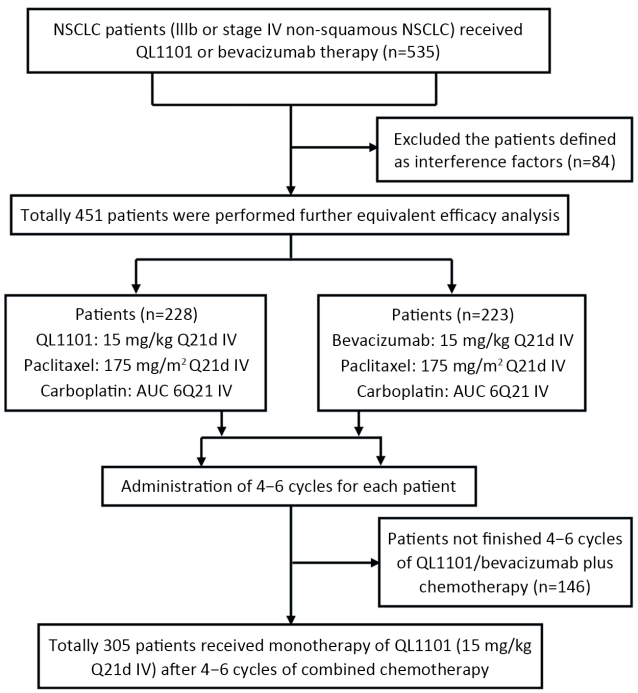

Figure 1 Study flowchart. NSCLC, non-small cell lung cancer; AUC, area under the curve.

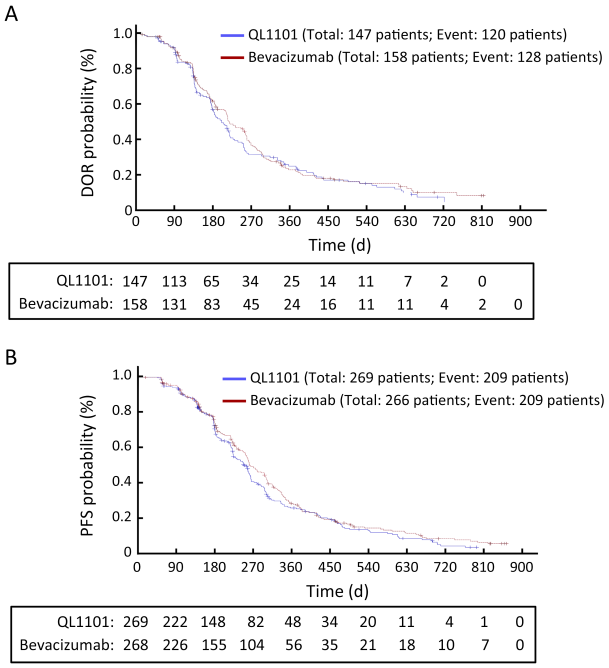

Figure 2 Equivalent efficacy analysis of QL1101 and bevacizumab in terms of DOR and PFS. (A) DOR equivalent evaluation: 120 patients had an event and a median DOR of 187 d in the QL1101 group; 128 patients had an event and a median DOR of 212 d in the bevacizumab group; (B) PFS equivalent evaluation: 269 patients were included in the QL1101 group, 209 of whom had an event and a median PFS of 242 d, and 266 patients were included in the bevacizumab group, 209 of whom had an event and a median PFS of 256 d. DOR, duration of response; PFS, progression-free survival.

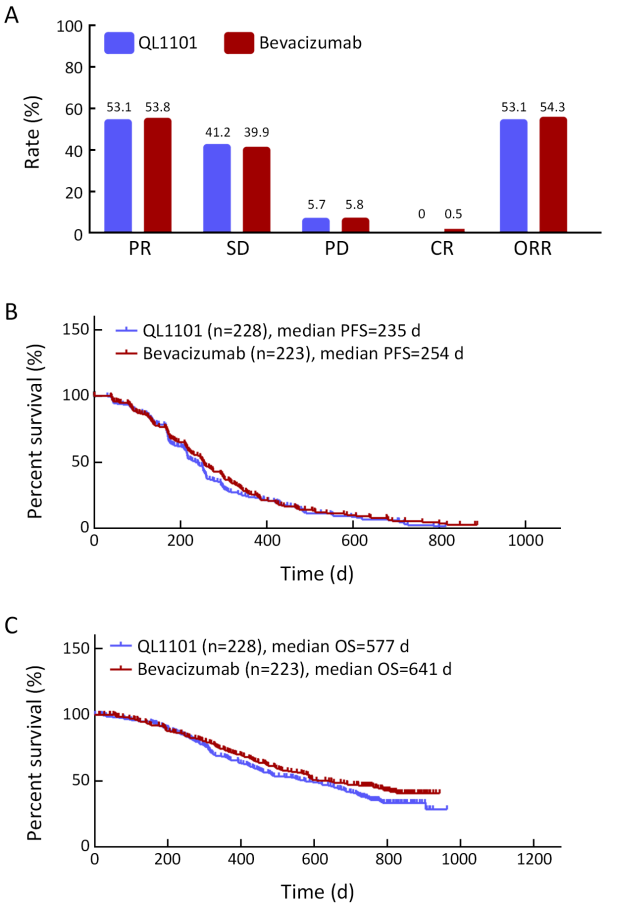

Figure 3 Evaluation of equivalent efficacy between QL1101 and bevacizumab after excluding interference factors (84 patients). (A) ORR equivalent evaluation: ORR (including CR, PR, SD and PD) was evaluated between the QL1101 group and the bevacizumab group; (B) PFS equivalent evaluation: 228 patients in the QL1101 group had a median PFS of 235 d; 223 patients in the bevacizumab group had a median PFS of 254 d; (C) OS equivalent evaluation: 228 patients in the QL1101 group had a median OS of 577 d; 223 patients in the bevacizumab group had a median OS of 641 d. ORR, objective response rate; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; PFS, progression-free survival; OS, overall survival.

in patients with a history of smoking or tumors contributed to the imbalance factors between the QL1101 group and the bevacizumab group. Therefore, we continued to exclude those 84 patients from further analysis (*Figure 1*). Of the remaining 451 patients, 228 were treated with QL1101, and 223 were treated with bevacizumab. The ORR analysis of the two groups showed that the PR rate was 53.1% *vs.* 53.8%, the SD rate was 41.2% *vs.* 39.9%, the PD rate was 5.7% *vs.* 5.8%, and the CR rate was 0 *vs.* 0.5%. The overall ORR was 53.1% in the QL1101 group and 54.3% in the bevacizumab group (QL1101 *vs.* bevacizumab: relative risk=0.977; 90% CI: 0.838–1.144) (*Figure 3A*). The PFS time of the QL1101 group and bevacizumab group was 235 d and 254 d, respectively (log-rank P=0.311; Chi-square=1.029) (*Figure 3B*). The OS time of QL1101 and bevacizumab was 577 d and 641 d, respectively (log-rank P=0.099; Chi-square=2.715) (*Figure 3C*). Efficacy analysis showed a mean tumor shrinkage of 22.5% in 228 patients treated with QL1101 and 23.5% in 223 patients treated with bevacizumab (*Figure 4A,B*). There was no significant difference between the two groups.

We further compared the efficacy of QL1101 and bevacizumab based on the difference in clinical characteristics (*Table 1*). For patients aged <65 years, the PFS and OS time were 251 d and 654 d for QL1101 and 254 d and 775 d for bevacizumab, respectively, with no significant difference between the two groups. For patients

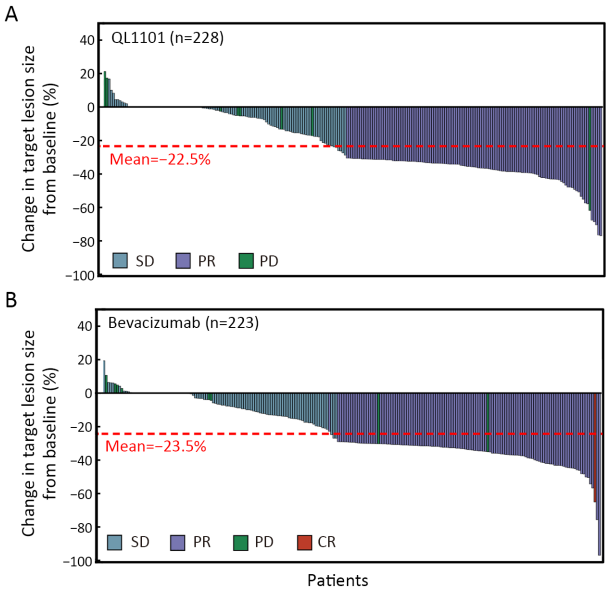

Figure 4 Analysis of tumor shrinkage in NSCLC patients after receiving QL1101 plus chemotherapy or bevacizumab plus chemotherapy. (A) Waterfall plot of the best response in NSCLC patients who received QL1101 plus chemotherapy. IRC-assessed best percentage change from baseline in target lesion size for the QL1101 group (n=228); (B) Waterfall plot of best response in NSCLC patients who received bevacizumab plus chemotherapy. IRC-assessed best percentage change from baseline in target lesion size for the bevacizumab group (n=223). NSCLC, non-small cell lung cancer; IRC, independent review committee; SD, stable disease; PR, partial response; PD, progressive disease; CR, complete response.

aged ≥65 years, the PFS and OS time was 216 d and 346 d for QL1101 and 231 d and 493 d for bevacizumab, respectively, with no significant difference between the two groups. Based on sex difference, we found that PFS was 217 d *vs.* 222 d for males and 268 d *vs.* 312 d for females; OS was 393 d *vs.* 497 d for males and 739 d *vs*. 807 d for females. There were no significant differences between the two groups in terms of sex except OS outcome for males (*Table 1*).

Categorized by smoking history, we found that patients with a history of smoking had a PFS of 217 d *vs.* 196 d and an OS of 393 d *vs*. 488 d when treated with QL1101 *vs.* bevacizumab. Patients without a history of smoking had a PFS of 253 d *vs*. 257 d and an OS of 687 d *vs.* 825 d when treated with QL1101 *vs.* bevacizumab. There was no significant difference in either PFS or OS between the two groups in terms of smoking history. According to *EGFR* mutation status, PFS was 223 d *vs.* 293 d for *EGFR*-positive patients treated with QL1101 *vs.* bevacizumab, and OS endpoint was not reached. PFS was 235 d *vs.* 246 d for *EGFR*-negative patients, and OS was 451 d *vs.* 504 d. There was no significant difference between the two groups. In addition, we did not find a significant difference in efficacy between QL1101 and bevacizumab based on the difference in tumor history and ECOG score (*Table 1*).

To further investigate the safety of QL1101 and bevacizumab, we compared the differences in side effects from different perspectives. Among 228 patients who received QL1101, 94 had grade 1 adverse reactions, 71 had grade 2 adverse reactions, and 19 had grade 3 adverse reactions. Among 223 patients treated with bevacizumab, 54 had grade 1 adverse reactions, 41 had grade 2 adverse reactions, and 21 had grade 3 adverse reactions. No grade 4 or higher adverse reactions were observed in either of the groups. The overall incidence of grade 3 adverse reactions was low and similar, indicating that both QL1101 and bevacizumab have favorable safety profiles (*Table 2*).

Equivalent efficacy analysis between QL1101 and bevacizumab in patients who received maintenance therapy

The maintenance phase of treatment was also a prominent aspect. Therefore, we further analyzed all patients who had completed 6 cycles of combined chemotherapy and began to receive maintenance therapy. A total of 157 patients in the QL1101 group received maintenance therapy, and a total of 148 patients in the bevacizumab group received maintenance therapy. PFS of patients receiving QL1101 was 253 d, and that of patients receiving bevacizumab was 272 d (log-rank P=0.387; Chi square=0.747). OS was 673 d for patients receiving QL1101 and 790 d for patients receiving bevacizumab (log-rank P=0.101; Chi square=2.697), with no significant difference between the two groups in either PFS or OS (*Figure 5A*). Further efficacy analysis yielded a mean tumor shrinkage of 26.6% in the 157 patients treated with QL1101 who received maintenance therapy and 27.5% in the 148 patients treated with bevacizumab who received maintenance therapy, with no significant difference between the two groups (*Figure 5B*).

In addition, we further analyzed patients who received maintenance therapy based on clinical characteristics. The results showed that in terms of clinical factors such as age, sex, smoking history, *EGFR* mutation status, tumor history and ECOG score, there was no significant difference in

Table 1 Equivalent therapeutic efficacy between QL1101 and bevacizumab was evaluated for subgroups of baseline characteristics

Variable	PFS (d)				OS (d)			
	QL1101#	Bevacizumab##	HR (95% CI)	P*	QL1101#	Bevacizumab##	HR (95% CI)	P*
Age (year)								
<65	251	254	1.070 (0.841–1.360)	0.582	654	775	1.204 (0.898–1.614)	0.216
≥65	216	231	1.221 (0.798–1.869)	0.357	346	493	1.432 (0.898–2.256)	0.133
Gender								
Male	217	222	1.001 (0.762–1.315)	0.996	393	497	1.384 (1.016–1.887)	0.040
Female	268	312	1.237 (0.889–1.721)	0.206	739	807	1.092 (0.724–1.647)	0.676
Smoking history								
Yes	217	196	1.020 (0.746–1.396)	0.900	393	488	1.186 (0.834–1.686)	0.343
No	253	257	1.164 (0.878–1.542)	0.291	687	825	1.261 (0.892–1.785)	0.190
EGFR mutation								
Yes	223	293	1.195 (0.789–1.812)	0.401	Undefined	Undefined	1.498 (0.854–2.628)	0.158
No	235	246	1.100 (0.863–1.401)	0.443	451	504	1.157 (0.879–1.524)	0.297
Tumor history								
Yes	253	276	1.405 (0.584–3.383)	0.448	714	691	0.865 (0.353–2.136)	0.753
No	234	251	1.101 (0.886–1.367)	0.385	555	641	1.261 (0.975–1.629)	0.077
ECOG								
0	242	272	0.904 (0.576–1.419)	0.662	653	Undefined	1.420 (0.807–2.500)	0.223
1	223	251	1.207 (0.951–1.533)	0.123	573	579	1.175 (0.893–1.547)	0.249

ECOG, Eastern Cooperative Oncology Group; PFS, progression-free survival; OS, overall survival; HR, hazard ratio; 95% CI, 95% confidence interval; #, bevacizumab biosimilar sourced from Qilu Pharmaceutical Co., Ltd, China; ##, bevacizumab sourced from Roche China; *, log-rank (Mantel-Cox) test P value.

Table 2 QL1101-induced *vs*. bevacizumab-induced treatment-related adverse events in advanced NSCLC patients

Adverse events	No. of patients									
	QL1101 group (N=228)					Bevacizumab group (N=223)				
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Leukopenia	15 (7%)	22 (10%)	12 (5%)	0	0	3 (1%)	17 (8%)	15 (7%)	0	0
Thrombocytopenia	10 (4%)	4 (2%)	2 (<1%)	0	0	5 (2%)	3 (1%)	3 (1%)	0	0
Anemia	11 (5%)	11 (5%)	1 (<1%)	0	0	8 (4%)	2 (<1%)	0	0	0
Alopecia	9 (4%)	16 (7%)	0	0	0	4 (2%)	9 (4%)	0	0	0
Nausea	10 (4%)	2 (<1%)	0	0	0	4 (2%)	3 (1%)	0	0	0
Vomiting	8 (3.5%)	1 (<1%)	0	0	0	1 (<1%)	2 (<1%)	0	0	0
Diarrhea	1 (<1%)	5 (2%)	0	0	0	4 (2%)	3 (1%)	0	0	0
Constipation	2 (<1%)	0	0	0	0	5 (2%)	0	0	0	0
Abdominal distension	1 (<1%)	3 (1%)	2 (<1%)	0	0	1 (<1%)	0	0	0	0
Fatigue	0	0	0	0	0	0	0	1 (<1%)	0	0
Sensory neuropathy	1 (<1%)	2 (<1%)	0	0	0	0	0	0	0	0
Poor appetite	14 (6%)	2 (<1%)	0	0	0	8 (4%)	0	1 (<1%)	0	0
Neuropathy	1 (<1%)	0	0	0	0	0	0	0	0	0
Myalgia	3 (1%)	0	2 (<1%)	0	0	5 (2%)	0	0	0	0
Arthralgia	7 (3%)	3 (1%)	0	0	0	5 (2%)	2 (<1%)	0	0	0
Hyponatremia	1 (<1%)	0	0	0	0	1 (<1%)	0	1 (<1%)	0	0

NSCLC, non-small cell lung cancer.

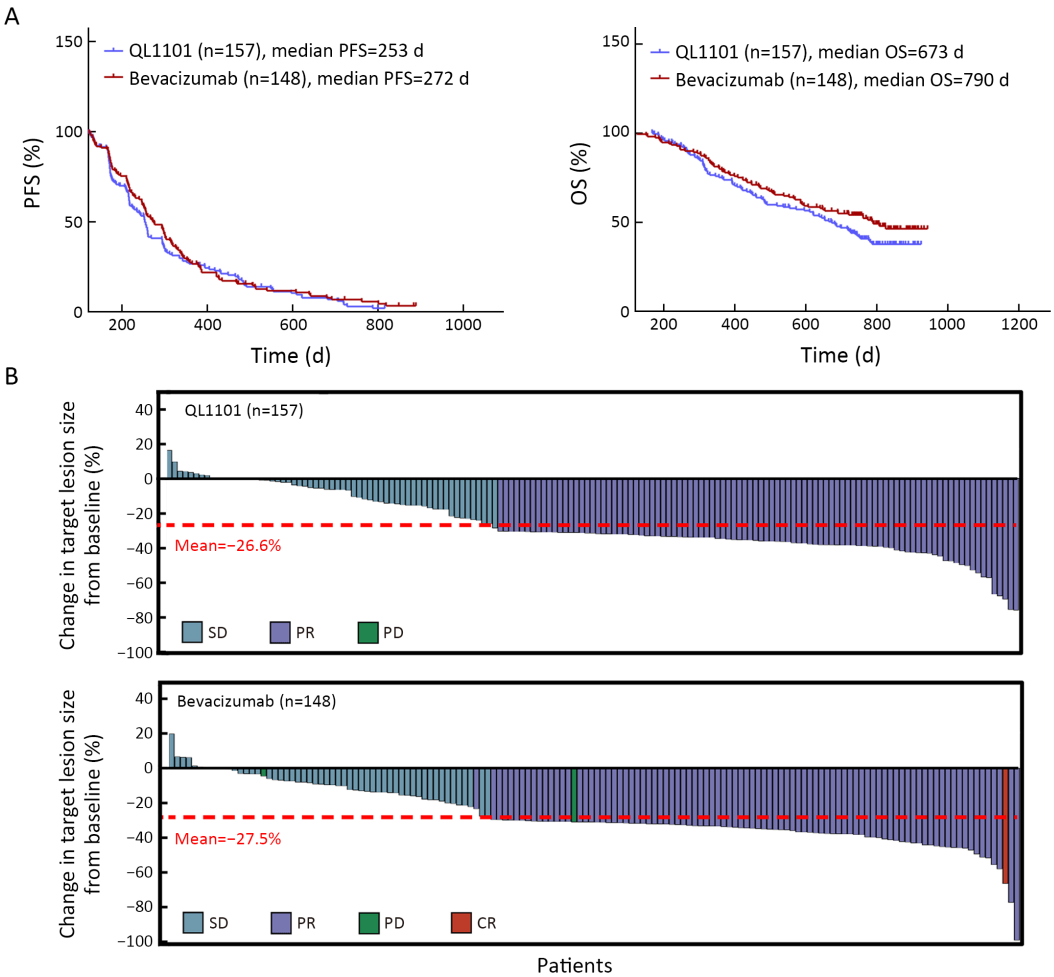

Figure 5 Evaluation of equivalent efficacy for NSCLC patients who received QL1101 maintenance therapy. (A) PFS equivalent evaluation: 157 patients in the QL1101 group had a median PFS of 253 d, and 148 patients in the bevacizumab group had a median PFS of 272 d. OS equivalent evaluation: 157 patients in the QL1101 group had a median OS of 673 d, and 148 patients in the bevacizumab group had a median OS of 790 d; (B) Waterfall plot of best response in NSCLC patients who received QL1101 plus chemotherapy or bevacizumab plus chemotherapy. The IRC assessed the best percentage change from baseline in target lesion size. NSCLC, non-small cell lung cancer; PFS, progression-free survival; OS, overall survival; IRC, independent review committee; SD, stable disease; PR, partial response; PD, progressive disease; CR, complete response.

efficacy between QL1101 and bevacizumab, except for OS of male patients in the analysis based on sex (*Table 3*). In terms of drug-induced adverse reactions, among the 157 patients who received QL1101, 65 had grade 1 adverse reactions, 57 had grade 2 adverse reactions, and 15 had grade 3 adverse reactions. Among the 148 patients who received bevacizumab, 37 had grade 1 adverse reactions, 24 had grade 2 adverse reactions, and 16 had grade 3 adverse reactions. No grade 4 or higher adverse reactions were observed in either of the groups. The overall incidence of grade 3 adverse reactions was low and similar, indicating that both QL1101 and bevacizumab have favorable safety profiles for patients who received maintenance therapy (*Table 4*).

Discussion

A total of 535 patients with stage IIIb or stage IV nonsquamous NSCLC were enrolled in this study and were equally assigned to the QL1101 and bevacizumab groups according to a 1:1 random assignment. We updated the 2-year follow-up results in this study.

Table 3 Equivalent therapeutic efficacy between QL1101 and bevacizumab was evaluated for patients received maintenance treatment

Variable	PFS (d)				OS (d)			
	QL1101#	Bevacizumab##	HR (95% CI)	P*	QL1101#	Bevacizumab##	HR (95% CI)	P*
Age (year)								
<65	255	272	1.079 (0.813–1.433)	0.599	717	Undefined	1.330 (0.922–1.918)	0.127
≥65	240	293	1.193 (0.734–1.941)	0.476	459	570	1.316 (0.753–2.299)	0.336
Gender								
Male	228	246	1.046 (0.759–1.443)	0.783	459	641	1.498 (1.019–2.200)	0.040
Female	298	314	1.115 (0.760–1.634)	0.579	Undefined	Undefined	1.055 (0.636–1.751)	0.837
Smoking history								
Yes	234	231	1.134 (0.777–1.656)	0.514	475	586	1.372 (0.879–2.143)	0.164
No	260	300	1.065 (0.771–1.472)	0.701	750	Undefined	1.182 (0.776–1.802)	0.436
EGFR mutation								
Yes	260	300	1.026 (0.643–1.659)	0.917	754	Undefined	1.789 (0.918–3.487)	0.088
No	252	257	1.182 (0.863–1.401)	0.443	638	641	1.148 (0.814–1.620)	0.432
Tumor history								
Yes	301	326	1.873 (0.662–5.304)	0.237	750	825	1.066 (0.357–3.185)	0.909
No	253	271	1.084 (0.840–1.398)	0.537	654	787	1.307 (0.951–1.798)	0.099
ECOG								
0	252	293	0.806 (0.477–1.363)	0.422	787	Undefined	1.398 (0.705–2.774)	0.919
1	255	266	1.249 (0.941–1.656)	0.124	665	761	1.254 (0.891–1.765)	0.194

ECOG, Eastern Cooperative Oncology Group; PFS, progression-free survival; OS, overall survival; HR, hazard ratio; 95% CI, 95% confidence interval; #, bevacizumab biosimilar sourced from Qilu Pharmaceutical Co., Ltd, China; ##, bevacizumab sourced from Roche China; *, log-rank (Mantel-Cox) test P value.

Table 4 QL1101-induced *vs.* bevacizumab-induced treatment-related adverse events in advanced NSCLC patients received maintenance treatment

Adverse events	No. of patients									
	QL1101 group (N=157)					Bevacizumab group (N=148)				
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Leukopenia	9 (6%)	19 (12%)	10 (6%)	0	0	3 (2%)	11 (7%)	13 (9%)	0	0
Thrombocytopenia	7 (4%)	4 (3%)	2 (1%)	0	0	3 (2%)	2 (1%)	2 (1%)	0	0
Anemia	10 (6%)	9 (6%)	1 (<1%)	0	0	6 (4%)	1 (<1%)	0	0	0
Alopecia	6 (4%)	10 (6%)	0	0	0	2 (1%)	7 (5%)	0	0	0
Nausea	6 (4%)	1 (<1%)	0	0	0	3 (2%)	1 (<1%)	0	0	0
Vomiting	3 (2%)	1 (<1%)	0	0	0	1 (<1%)	0	0	0	0
Diarrhea	1 (<1%)	4 (3%)	0	0	0	4 (3%)	1 (<1%)	0	0	0
Constipation	1 (<1%)	0	0	0	0	1 (<1%)	0	0	0	0
Abdominal distension	1 (<1%)	3 (2%)	0	0	0	0	0	0	0	0
Fatigue	0	0	0	0	0	0	0	0	0	0
Sensory neuropathy	0	2 (1%)	0	0	0	0	0	0	0	0
Poor appetite	9 (6%)	1 (<1%)	0	0	0	7 (5%)	0	0	0	0
Neuropathy	1 (<1%)	0	0	0	0	0	0	0	0	0
Myalgia	3 (2%)	0	2 (1%)	0	0	3 (2%)	0	0	0	0
Arthralgia	7 (4%)	3 (2%)	0	0	0	3 (2%)	1 (<1%)	0	0	0
Hyponatremia	1 (<1%)	0	0	0	0	1 (<1%)	0	1 (<1%)	0	0

NSCLC, non-small cell lung cancer.

Chemotherapy has played a crucial role in the long history of NSCLC treatment (5-7). To date, it remains one of the most prominent treatments for patients without driver genes (7). However, with the advancement of drug development, antiangiogenic therapy has become an increasingly important part of the treatment of NSCLC (18). The antiangiogenic hypothesis was first proposed by Folkman *et al.* in 1971, suggesting that tumor growth was reliant on neovascularization. Once this process is blocked, tumor growth will also be inhibited (19). In 1983, Senger *et al.* revealed that tumor-secreted VEGFA significantly promoted the production of ascites, suggesting that it could promote tumor progression (20). In 1992, more receptors, such as VEGFR1, VEGFR2, and VEGFRs, were successively identified (21). A year later, the first monoclonal antibody to neutralize VEGF was discovered (22). As the first antiangiogenic drug was successfully developed, bevacizumab was officially approved by the American Food and Drug Administration (FDA) for the treatment of NSCLC in 2006 (8), and since then, antiangiogenic therapy has been accepted by both physicians and patients (23). Due to high research and development (R&D) and pharmaceutical costs, despite offering many NSCLC patients the opportunity to extend their survival time, bevacizumab was only available to a limited number of patients in less developed countries (6,11-13). As technology advances, following the expiration of patent protection for bevacizumab, researchers have begun to design new protocols for the production of bevacizumab analogues to minimize the cost of bevacizumab production with the assurance of efficacy and safety. If these biosimilars are successful, it would significantly reduce the cost and benefit more patients in less developed regions, alleviating their financial burden to the greatest extent possible.

Since Amgen's first bevacizumab biosimilar was approved by the FDA (15,16), Qilu's QL1101 was also approved for clinical use by the China NMPA in 2019 (6). The launch of these drugs accelerates market competition, lowers drug prices, helps diversify market offerings and reduces the financial burden of patients. We have reported the one-year follow-up results, while the results of the two-year follow-up are still unclear. In this study, we further analyzed the results of the two-year follow-up. First, it was clear that there were no significant differences in the DOR and PFS between QL1101 and bevacizumab. Based on our prior study, we excluded data from 81 patients who had characteristics that may interfere with the analysis of OS. The results showed that there was no significant difference in either PFS or OS between QL1101 and bevacizumab in the treatment of NSCLC patients. Further analysis of tumor shrinkage showed good agreement between QL1101 and bevacizumab. In terms of drug-induced side effects, both QL1101 and bevacizumab had similar rates of grade 3 and higher adverse reactions, with no significant difference between the two groups. In addition, the analysis of patients receiving maintenance therapy revealed that there were no significant differences between QL1101 and bevacizumab in terms of PFS, OS, tumor shrinkage and adverse effects. Interestingly, the analysis of OS in males showed that bevacizumab had a significantly higher OS than QL1101. This could be due to the different treatment choices of patients after exiting the group.

Conclusions

This study reports the results of a two-year follow-up of a bevacizumab biosimilar, QL1101. The results of this study demonstrated that QL1101 had similar efficacy in treating nonsquamous NSCLC in terms of ORR, PFS, OS and side effects, providing a basis for the clinical application of QL1101.

Acknowledgements

This study was supported by the foundation of Chinese Society of Clinical Oncology (No. Y-2019AZZD-0355 & Y-QL2019-0125); the foundation of Shanghai Chest Hospital (No. 2019YNJCM11); and the program of system biomedicine innovation center from Shanghai Jiao Tong University (No. YG2021QN121).

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Lu J, Chu T, Liu H, Hu M, Lou Y, Zhang Y, Gao Z, Zhang W, Zhang X, Wang H, Zhong H, Han B. Equivalent efficacy assessment of QL1101 and bevacizumab in nonsquamous non-small cell lung cancer patients: A two-year follow-up data update. Chin J Cancer Res 2022;34(1):28-39. doi: 10.21147/j.issn.1000-9604.2022.01.03

