BMC Cancer

RESEARCH Open Access

First-line treatment with gefitinib in combination with bevacizumab and chemotherapy in advanced non-squamous NSCLC with *EGFR*-mutation

Yanjuan Xiong[1,2,3,4,5†], Lu Wang[1,2,3,4,6,8†], Weihong Zhang[1,2,3,4,5], Yuan Meng[1,2,3,4,6], Yang Wang[1,2,3,4,5], Meng Shen[1,2,3,4,5], Li Zhou[1,2,3,4,5], Runmei Li[1,2,3,4,5], Yingge Lv[1,2,3,4,6], Shengguang Wang[1,2,3,4,7*], Xiubao Ren[1,2,3,4,5,6*] and Liang Liu[1,2,3,4,5*]

Abstract

Background The safety and efficacy of combination of gefitinib with chemotherapy and bevacizumab in treatment patients with epidermal growth factor receptor *(EGFR)* mutations are currently unknown. This study was designed to evaluate the safety and preliminary efficacy of a combination therapy consisting of gefitinib, bevacizumab, pemetrexed, and carboplatin in patients with advanced non-squamous non–small cell lung cancer (NSCLC) harboring *EGFR* mutations.

Methods Eligible patients with *EGFR*-mutated advanced non-squamous NSCLC were recruited and received gefitinib combination with bevacizumab plus pemetrexed and carboplatin treatment. The primary endpoints were safety and progression-free survival (PFS). Secondary endpoints included objective response rate (ORR), disease control rate (DCR), duration of response (DOR), and overall survival (OS).

Results From June 2019 to June 2021, 20 patients were enrolled in this study. The median follow-up was 33.8 months (95% CI, 31.0-36.6). Grade ≥ 3 adverse events was 65%, including neutropenia (30%), thrombocytopenia (20%), nausea (20%), skin rash (20%), bleeding (10%), and increased ALT (10%). There was no death related to toxicity occurred. The median PFS was 28 months (95% CI, 20.4–35.6). the ORR was 95% (95% CI, 75.1-99.9%), the DCR was 100% (95% CI, 83.2-100%), and the median DOR was 26.4 months (95% CI, 18.9–33.9). The median OS has not been reached.

Conclusion The results of this study demonstrate that the four-drug combination regimen, led by gefitinib, is manageable and tolerated and effective for patients with *EGFR*-mutated advanced non-squamous NSCLC.

Keywords Non-squamous non–small cell lung cancer, *EGFR* mutation, Gefitinib, Bevacizumab, Chemotherapy

†Yanjuan Xiong and Lu Wang contributed equally to this work.

*Correspondence:
Shengguang Wang
wangshengguang@tjmuch.com
Xiubao Ren
renxiubao@tjmuch.com
Liang Liu
liuliang@tjmuch.com

Full list of author information is available at the end of the article

Introduction

Primary bronchogenic carcinoma is one of the most common and deadliest malignancies [1]. According to the latest data from 2020, lung cancer has the second highest incidence rate (11.4%) among all malignant tumors worldwide, and it ranks first in terms of mortality rate (18.0%) (1). Non-small cell lung cancer (NSCLC) is the most common histological type of lung cancer, accounting for 80–85% of all malignant lung tumors, with non-squamous histology representing approximately 40% of all NSCLC cases [2]. For patients with advanced-stage (IIIB-IV) NSCLC, platinum-based chemotherapy remains the standard treatment regimen [3–6]. However, studies have shown that approximately 15% of Caucasian and nearly 50% of Asian patients with advanced NSCLC have epidermal growth factor receptor (*EGFR*) mutations [7]. Several large-scale Phase III clinical trials have consistently demonstrated that first generation tyrosine kinase inhibitors (TKIs) such as gefitinib and erlotinib, exhibit superior efficacy compared to standard first-line platinum-based chemotherapy in patients with advanced NSCLC harboring *EGFR* mutations [8–11]. Unfortunately, despite the effectiveness of EGFR TKI monotherapy in these patients, most of them inevitably develop resistance, with a median progression-free survival (PFS) ranging from 9 to 13 months [8, 12]. Therefore, there is an urgent need to develop new treatment strategies to further improve the overall survival of patients with advanced non-squamous NSCLC harboring *EGFR* mutations.

Currently, the combination of EGFR TKIs with bevacizumab or cytotoxic chemotherapy has received widespread attention [13]. The NEJ009 Study demonstrated that in *EGFR* mutation-positive NSCLC patients treated with the combination of chemotherapy and gefitinib, the objective response rate (ORR) (84% vs. 67%) and PFS (20.9 months vs. 11.9 months) were significantly higher compared to patients receiving gefitinib monotherapy [14]. In NEJ026 study, the results showed that the median PFS for patients in the erlotinib plus bevacizumab group was 16.9 months compared with 13.3 months for patients in the erlotinib group [hazard ratio (HR) 0.605, 95% CI 0.417–0.877; $P=0.016$)], and indicated that the combination of erlotinib and bevacizumab appears to be a favorable and well-tolerated treatment option for first-line therapy in advanced NSCLC patients with *EGFR* mutations [15].

TP53 mutations co-occurring with *EGFR* mutations are very common in NSCLC [16–18]. The CTONG 0901 study [19] revealed that in patients with *EGFR*-mutated NSCLC treated with EGFR-TKIs, the presence of *TP53* mutations was associated with a median PFS of 10.7 months, compared to a notably longer median PFS of 14.5 months for those without *TP53* mutations. While Canale's [20] research indicated that there was no statistically significant difference in PFS and overall survival (OS) between patients with *TP53* mutations and without *TP53* mutations. Previous studies have concentrated on how specific *TP53* mutations within certain exons might affect the response to EGFR TKIs, yielding inconsistent results [19–22]. This has fueled ongoing debates about the prognostic value of *TP53* mutations in *EGFR*-mutated NSCLC and has stimulated interest in exploring combined EGFR therapies for patients with *TP53* mutations.

However, little is known about the safety and efficacy of combination of four drugs (first generation EGFR-TKI, bevacizumab, and platinum-based dual drug chemotherapy) in treatment NSCLC patients with *EGFR* mutations. Based on these findings, we proposed a regimen combining gefitinib, bevacizumab, pemetrexed, and carboplatin, and planned to conduct a clinical study to determine its clinical safety and preliminary efficacy.

Patients and methods

Patient population

The study was conducted following the principles of the Helsinki Declaration, and written informed consent was obtained from all patients prior to enrollment. The main inclusion criteria were as follows: males or females aged between 18 and 70 years old; Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 within 7 days prior to randomization; untreated patients diagnosed with stage IIIB/IIIC/IV non-squamous NSCLC; confirmed *EGFR* mutations including 19del or L858R; ineligible for synchronous radiochemotherapy after multidisciplinary consultation; presence of at least one measurable objective tumor lesion with a maximum diameter ≥ 1 cm; and adequate organ function. The main exclusion criteria were serious concomitant systemic disorders, interstitial pneumonia, another primary malignancy, preexistence of T790M mutation, symptomatic brain metastases, high risk of bleeding or coagulation disorders, and pregnancy.

Study design and treatment

In this clinical trial, during the induction phase, each treatment cycle occurs every 3 weeks (Fig. 1). Patients received daily oral administration of gefitinib (250 mg). On the first day of each cycle, they received intravenous infusion of bevacizumab (7.5 mg/kg), pemetrexed (500 mg/m^2), and carboplatin [area under the curve (AUC) = 5)]. After 4 cycles, the induction treatment is completed, and carboplatin is discontinued. Maintenance therapy continues with the combination of gefitinib, bevacizumab, and pemetrexed (using the same dosage, route, and frequency). After 2 years, bevacizumab and pemetrexed are discontinued, and gefitinib maintenance

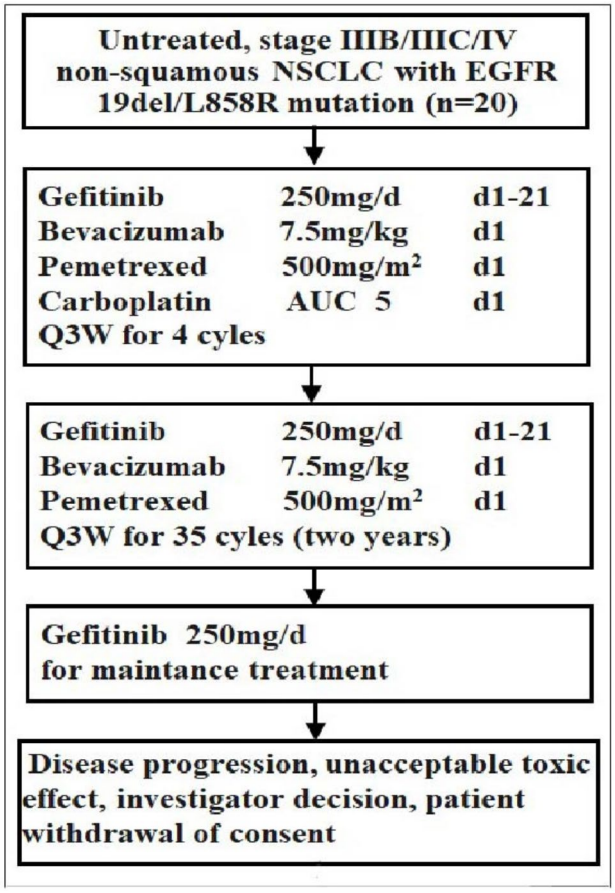

Fig. 1 CONSORT diagram for this clinical trial. NSCLC, non-small cell lung cancer; *EGFR*, epidermal growth factor receptor; AUC, area under the curve; Q3W, every 3 weeks for one cycle; PD, progressive disease

therapy is continued. Administration continues until disease progression, intolerable toxicity, voluntary withdrawal by the subject, or the investigator determines the subject's need to exit the study, with precedence given to the earliest occurrence.

Safety evaluation

During the treatment period, vital signs, physical examinations, hematological and clinical chemistry tests, and quality of life assessments should be obtained prior to each dose administration, at the end of each treatment visit, and when clinically significant. The safety evaluation will be conducted by recording all adverse events (AEs) in the case report form. Laboratory test results, vital signs, and physical examination findings that are clinically significant will be documented as AEs. In the event of a serious adverse event, the provided form by the sponsor should be used for reporting. Adverse events will be described using the Medical Dictionary for Regulatory Activities (MedDRA) terminology and graded according to the NCI-CTCAE v5.0.

Efficacy evaluation

The objective response rate (ORR), disease control rate (DCR), duration of response (DOR), progression-free survival (PFS), and overall survival (OS) of all enrolled subjects receiving the treatment regimen will be evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST 1.1). Radiographic assessments were performed at baseline and then every 6 weeks for the first year and every 2 months thereafter until disease progression (PD). PFS was defined as the time from treatment initiation to disease progression or death from any cause. OS was defined as the time from the start of treatment until death from any cause.

TP53 destructive/non-destructive mutations

Previous studies focused on the impact of *TP53* mutations within a certain exon on EGFR TKI efficacy and the results were inconsistent [16–20]. This may suggest that the number of exons that harbors the mutations is not a reliable predictor for the impact on TKI efficacy. In some studies, *TP53* mutations have been classified into destructive and non-destructive types [16, 21, 22]. Therefore, we introduced the concept of *TP53* disruptive/non-disruptive mutations in this study to explore whether the effect of *TP53* mutations on TKI efficacy.

Statistical methods

The primary endpoints were safety and PFS. Secondary endpoints included ORR, DCR, DOR, and OS. Sample size of the study was determined on PFS. According to the results of NEJ009 [14], the median PFS of gefitinib in advanced NSCLC patients with *EGFR* mutation is about 10.0 months. The median PFS of gefitinib combination with bevacizumab, pemetrexed, and carboplatin is expected to reach 30 months. The recruitment of patients would be completed in two years. Patients would be followed up for two years until the last participant was enrolled. Assuming a 1-sided type I error of 0.05, a power of 80%, and considering the 10% drop-off rate, 21 patients were required in this study. The collected clinical data will be organized and subjected to statistical analysis using SPSS software (version 23.0). A waterfall plot depicting the best overall response will be generated using Excel. Swimmer's plots, as well as Kaplan-Meier survival curves for duration of response (DOR), PFS, and OS, will be constructed using GraphPad Prism (version 8.0).

Results

Patient characteristics

From June 2019 to June 2021, 20 patients were enrolled in this study, and their characteristics were summarized in Table 1. The median age of all patients was 58 years, with 12 males and 8 females. All patients enrolled in the

Table 1 Patient characteristics at baseline

Characteristic	Patients, No. (%)
Median age (range)	58 (26–68)
Sex	
Male	12 (60)
Female	8 (40)
Smoking status	
Never	9 (45)
Smoker	11 (55)
ECOG PS	
0	11 (55)
1	9 (45)
Histology	
Adenocarcinoma	20 (100)
Clinical stage	
IIIB	1 (5)
IIIC	1 (5)
IV	18 (90)
Distant metastasis status	
Yes	20 (100)
No	0 (0)
EGFR mutation type	
Exon 19 deletion	12 (60)
L858R	8 (40)
TP53 destructive mutation	
Yes	9 (45)
No	11 (55)

Abbreviations: ECOG PS: Eastern Cooperative Oncology Group performance status; *EGFR*: epidermal growth factor

Table 2 The profile of major AEs during the total period

Adverse Event	Patients, No. (%) (*N* = 20)	
	Any Grade	Grade 3–4
Any adverse event	20 (100)	13 (65)
Event leading to stop pemetrexed and bevacizumab and Gefitinib	1 (5)	1 (5)
Event leading to stop pemetrexed and bevacizumab	5 (25)	5 (25)
Event leading to stop pemetrexed	3 (15)	3 (15)
Event leading to stop bevacizumab	2 (10)	2 (10)
Event leading to death	0	0
Event		
Neutropenia	19 (95)	6 (30)
Thrombocytopenia	18 (90)	4 (20)
Hemoglobin reduction	18 (90)	0 (0)
Nausea	16 (80)	4 (20)
Skin rash	16 (80)	4 (20)
Asthenia	10 (50)	0 (0)
Vomiting	9 (45)	0 (0)
ALT increased	8 (40)	1 (5)
AST increased	8 (40)	0 (0)
Bleeding	6 (30)	2 (10)
Mouth ulceration	3 (15)	2 (10)
Hypertension	3 (15)	1 (5)
Diarrhea	2 (10)	0 (0)
Edema	1 (5)	0 (0)
Protein urine	1 (5)	0 (0)

Abbreviations: AE: adverse event; ALT: glutamic-pyruvic transaminase; AST: glutamic-pyruvic transaminase

study characterized by *EGFR* mutations. Molecular testing for these patients was conducted exclusively using next-generation sequencing(NGS) techniques provided by Genecast Biotechnology Co., Ltd(Wuxi, China). A comprehensive NGS panel, covering 769 cancer-related genes, was employed for hybridization-based sequencing (refer to Supplementary Table 1 for details) 0.12 (60%) patients had exon 19 deletion, and 8 (40%) patients had exon 21 L858R mutation. 9 (45%) patients had *TP53* gene destructive mutation.

receptor.

Safety

All patients enrolled in the study successfully completed the induction therapy phase. The median duration of exposure during the maintenance phase was 15.65 months for both bevacizumab and pemetrexed, with the range of exposure being 4 to 24 months, as further detailed in Supplementary Table 2. A comprehensive overview of adverse events (AEs) occurring throughout the treatment period is presented in Table 2. Notably, all 20 (100%) patients encountered AEs, with 13 (65%) experiencing grade 3–4 AEs.During the maintenance phase, one patient (5%) discontinued all medications, including gefitinib, bevacizumab, and pemetrexed, due to a recurrent grade 4 rash. Additionally, 9 (45%) patients discontinued bevacizumab and/or pemetrexed attributable to AEs. Hematological AEs of grade 3 or higher comprised neutropenia in 30% and thrombocytopenia in 20% of the patients. It is reassuring to report that no patients developed febrile neutropenia.Non-hematological grade 3 or higher AEs included nausea affecting 20%, skin rash in 20%, bleeding in 10%, mouth ulceration in 10%, hypertension in 5%, and elevated glutamic-pyruvic transaminase (ALT) in 5% of the patients. There were no fatalities associated with treatment-related toxicity.

Efficacy

The ORR was 95%, including 5% CR and 90% PR. The DCR was 100%. The waterfall plot, swimming plot, and spider plot were showed in Fig. 2. After 33.8-months (95% CI, 31.0-36.6) median follow-up, the median PFS was 28.0 months (95% CI, 20.4–35.6), median DOR was 26.4 months (95% CI, 18.9–33.9), and median OS was not reached (Fig. 3). The median PFS in patients with exon 19 deletion was 31.0 months (95% CI, 28.9–39.1), and in patients with exon 21 L858R was 20.5 months (95% CI, 10.6–30.4) (HR, 0.342; 95% CI, 0.100-1.169; P=0.074). The median OS was not reached in patients with exon

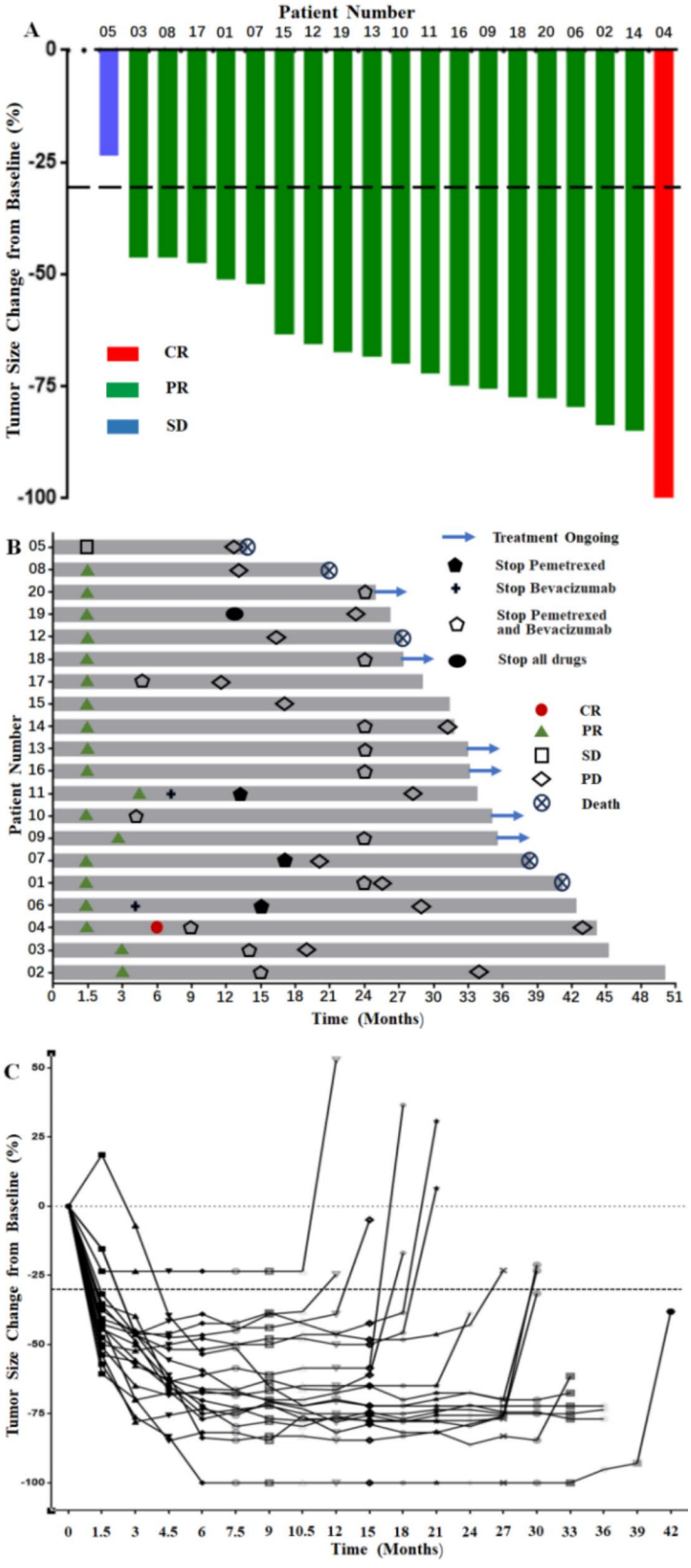

Fig. 2 (**A**) Waterfall plot: maximal change of tumor size from base line assessed by investigator per Response Evaluation Criteria in Solid Tumors (RECIST) version1.1 ($N=20$); (**B**) Swimming plot: exposure and duration of response per RECIST version 1.1; (**C**) Spider plot: change in individual tumor burden over time from baseline assessed by investigator per RECIST version 1.1. CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease

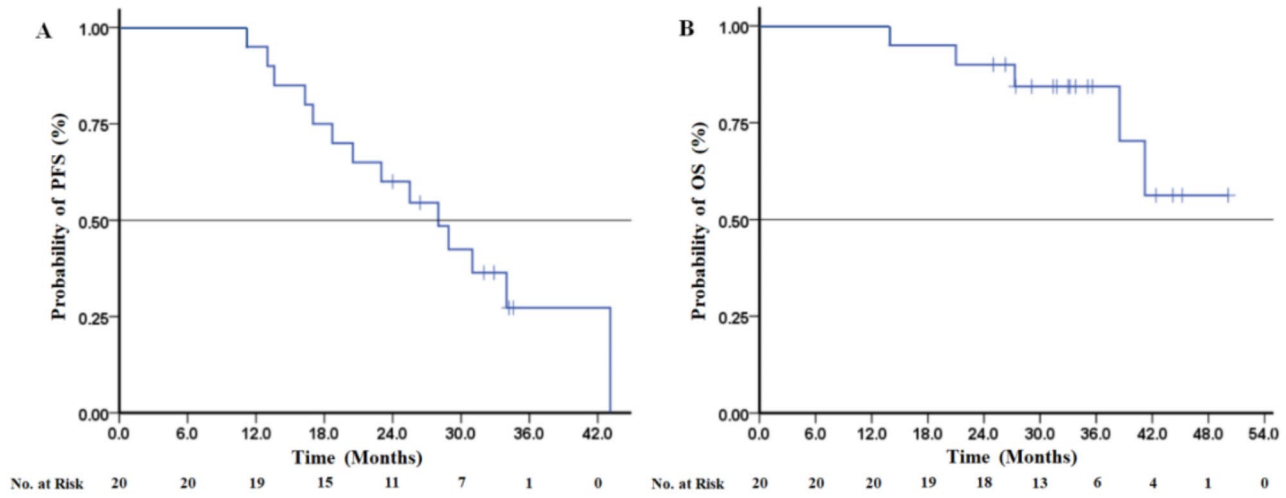

Fig. 3 (**A**) Progression-free survival, and (**B**) overall survival in this clinical trial by RECIST version 1.1. PFS, progression-free survival; OS, overall survival

19 deletion, and 41.2 months (95% CI, 36.8–45.6) in patients with exon 21 L858R (HR, 0.478; 95% CI, 0.079–2.882; $P=0.411$). The median PFS in patients with *TP53* destructive mutation and *TP53* non-destructive mutation were 17.0 months (95% CI, 15.0–19.0) and 34.0 months (95% CI, 27.7–40.3), respectively (HR, 0.331; 95% CI, 0.113–0.997; $P=0.048$). The median OS in patients with *TP53* destructive mutation and *TP53* non-destructive mutation were 41.2 months (95% CI, 27.3-NA) and not reached, respectively (HR, 0.110; 95% CI, 0.014–0.995; $P=0.022$) (Fig. 4).

Characteristics and efficacy of patients after PD

The cutoff date was August 31, 2023. 14 patients were disease progression, 6 patients are still received maintenance treatment with gefitinib at the cutoff date. 13 of 14 patients with disease progression received secondary next-generation sequencing (NGS) test. One patient quickly died due to brainstem metastasis and did not receive NGS test and treatment. One patient's pathological type transformed from lung adenocarcinoma to small cell lung cancer. 7 (7/14, 50%) patients had brain or meningeal metastasis. 8 (8/13, 62%) patients had *EGFR* exon 20 T790M mutation and received osimertinib or combination therapy. 5 patients without T790M mutation received chemotherapy or combination treatment (Supplementary Table 3). The PFS and OS were 10.5 months (95% CI, 7.5–13.5) and 18.0 months (95% CI, 13.5–22.5), respectively (Supplementary Fig. 1). The median PFS in patients with T790M mutation was 15.1 months (95% CI, 8.2–22.0), and in patients without T790M mutation was 8.5 months (95% CI, 1.3–15.7) (HR, 0.110; 95% CI, 0.011–0.926; $P=0.024$). The median OS in patients with T790M mutation was not reached, and in patients without T790M mutation was 15.7 months (95% CI, 8.2–23.2) (HR, 0.187; 95% CI, 0.019–1.807; $P=0.104$.) (Supplementary Fig. 2).

Discussion

To the best of our knowledge, this is the first study evaluating the safety and efficacy of gefitinib plus bevacizumab in combination with platinum-based doublet therapy in patients with advanced non-squamous NSCLC harboring *EGFR* mutations. After a 33.8-months median follow-up, the results demonstrated that this four-drug Most toxicities of the four-drug regimen were manageable and achieved the primary endpoint of a 28-months median PFS, as well as the secondary endpoints of a 95% ORR, a 100% DCR, and a 26.6-months median DOR. The median OS was not reached.

In terms of safety, two phase I dose-escalation studies conducted in 2017 have demonstrated the safety and feasibility of a four-drug combination consisting of EGFR-TKI (erlotinib) in combination with chemotherapy and anti-angiogenic agents [23, 24]. Previous studies have reported that the most common AEs associated with single agent gefitinib therapy are skin rash, elevated transaminases, and diarrhea [9, 25]. On the other hand, chemotherapy agents such as platinum-based drugs are known to cause hematological toxicities such as neutropenia and anemia [9, 26]. Furthermore, studies have shown that compared to single-agent gefitinib therapy, the combination of gefitinib with platinum-based doublet therapy slightly increases toxicity, but the toxicity is manageable and clinically controllable [26]. In our study, all grade≥3 AEs was 65%, including neutropenia (30%), thrombocytopenia (20%), nausea (20%), and skin rash (20%). When we compare these findings to the NEJ009

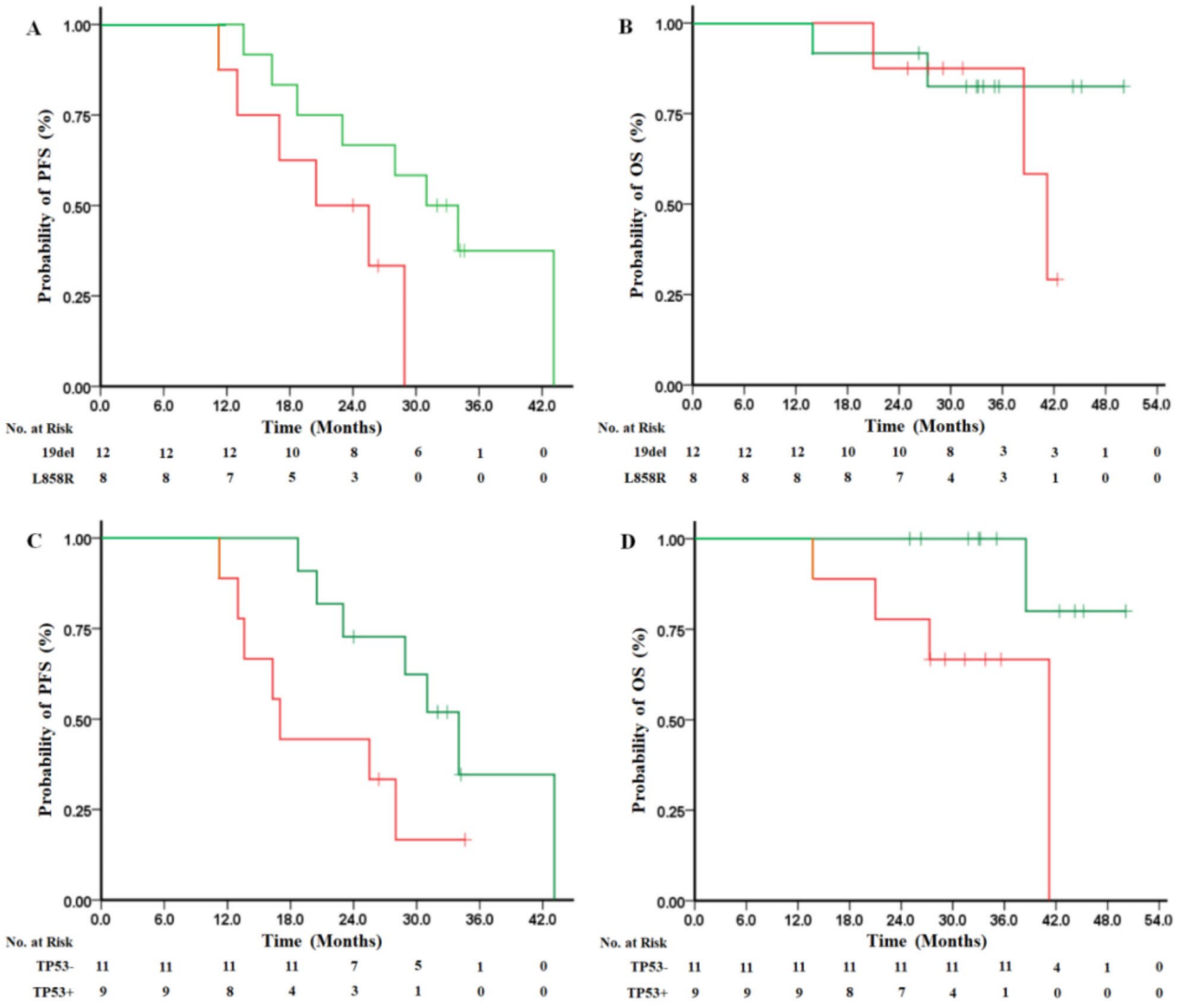

Fig. 4 (**A**) Progression-free survival, and (**B**) overall survival in patients with *EGFR* exon 19 deletion ($n=12$) and exon 21 L858R ($n=8$) by RECIST version 1.1; (**C**) Progression-free survival, and (**D**) overall survival in patients with *TP53* non-destructive mutation ($n=11$) and destructive mutation ($n=9$) by RECIST version 1.1. PFS, progression-free survival; OS, overall survival; *TP53*-, *TP53* non-destructive mutation; *TP53*+, *TP53* destructive mutation

Study [14], which reported a 65.3% incidence of grade 3 or higher toxicity with the triple-drug combination of gefitinib, pemetrexed, and cisplatin, the rates of grade 3/4 AEs in our study appear comparable. These results indicated that the toxicity of our four-drug combination study did not exhibit significant cumulative effects, and most toxicities were reversible. Therefore, we consider the four-drug combination regimen consisting of gefitinib as the foundation, combined with bevacizumab and chemotherapy agents, to be both manageable and tolerated.

Recently, combination therapy based on the EGFR-TKI gefitinib has demonstrated superior efficacy compared to single-agent gefitinib treatment in the NEJ009 study [14, 27]. In this study, the gefitinib, bevacizumab, pemetrexed, and carboplatin four-drug combination therapy established for the enrolled 20 patients achieved an ORR of 95%, and a median PFS of 28 months (95% CI: 20.43–35.57). Compared to the currently established median PFS of gefitinib-based combination therapies [20.9 months in gefitinib plus pemetrexed and carboplatin [14];15.8 months in gefitinib plus pemetrexed [28]; 16.0 months in gefitinib plus pemetrexed and carboplatin [29]], the observed PFS in this study was more promising. On one hand, the combination of gefitinib and bevacizumab simultaneously inhibits both EGFR and VEGF, further attenuating the proliferative capacity of tumor endothelial cells [30]. Additionally, bevacizumab inhibits

the formation and growth of new blood vessels, normalizes the vascular system, facilitates drug delivery, also exerts direct effects on tumor cells [30]. On the other hand, platinum-based drugs effectively inhibit the development of wild-type *EGFR* NSCLC, while EGFR-TKIs effectively suppress the development of *EGFR*-mutant NSCLC [31, 32]. Due to the genetic heterogeneity of tumors, early treatment with EGFR TKIs and platinum-based doublet therapy can restrain the growth of both wild-type *EGFR* and *EGFR*-mutant cells, thereby more effectively limiting tumor progression [33, 34]. Previous studies had reported that *EGFR* exon 21 L858R mutation patients had poorer prognosis than exon 19 deletion patients [28–30], and *TP53* mutation patients had poorer prognosis than *TP53* wild-type patients [18–21]. These conclusions had also been confirmed in our small sample clinical study (Fig. 4). But the combination of four drugs in our study could still prolong the survival of patients with *EGFR* exon 21 L858R mutation or *EGFR* mutation accompanying *TP53* destructive mutation, as compared with only first-generation EGFR-TKI treatment [16, 19–21, 28–30].

After the progression of first-generation EGFR-TKI treatment in patients with *EGFR* mutation, about 60% of patients are found to have a T790M point mutation. The median PFS for second-line osimertinib treatment is 11.1 months and for platinum therapy plus pemetrexed is 4.4 months [35]. In our study, the incidence of acquired mutation of T790M was 62% (8/13) after disease progression of four-drug combination treatment, and the median PFS for second-line osimertinib treatment was 15.1 months. The median PFS for second-line chemoradiotherapy in patients without T790M mutation was 8.5 months (Supplementary Fig. 2). These results showed that the combination treatment of four drugs had no effect on the incidence of T790M acquired mutation and the efficacy of second-line treatment.

Conclusion

In summary, the four-drug combination regimen of gefitinib, bevacizumab, carboplatin, and pemetrexed in this study is safety and effective for patients with advanced non-squamous NSCLC harboring *EGFR* mutations. Our clinical study results indicate that the four-drug combination therapy holds promise and merits further investigation.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-024-13084-x.

Supplementary Material 1

Acknowledgements

We gratefully acknowledge the support from Tianjin Key Medical Discipline(Specialty) Construction Project (TJYXZDXK-009 A) and the National Natural Science Foundation of China. Grants Awards No. 81872487 (to Liang Liu). Our thanks go to the Tianjin Medical University Cancer Institute & Hospital and Jiujiang No.1 People's Hospital for their technical assistance and resources. We also extend our appreciation to all participants who contributed to this study. The abstract of this manuscript, has been previously presented at the "American Society of Clinical Oncology Annual Meeting",for more details, please refer to https://ascopubs.org/doi/10.1200/JCO.2024.42.16_suppl.8554. We express our gratitude to for their support and contributions to this research.

Author contributions

Liang liu, Xiubao Ren and Shengguang Wang conceived the original idea for the study and was responsible for the overall project supervision. They were also involved in the experimental design, data analysis, and contributed significantly to the writing of the manuscript. They were responsible for the final review of the manuscript before submission. They ensured that all authors met the criteria for authorship and that the manuscript was ready for publication. Yanjuan Xiong and Lu Wang conducted the experiments and collected the data. They were responsible for the methodology section of the paper and provided critical feedback on the draft and helped shape the research, analysis, and manuscript. Meng Shen, Yuan Meng and Yang Wang performed the statistical analysis of the data and helped in interpreting the results. They were also involved in drafting the results section of the manuscript and contributed to the discussion of the findings. Weihong Zhang and LiZhou contributed to the acquisition of funding and resources for the project. They were involved in the conceptualization of the study and provided guidance on the theoretical framework. Runmei Li and Yingge lv assisted with the literature review and provided insights into the broader implications of the study. They were also responsible for the editing and proofreading of the manuscript. All authors have read and approved the final manuscrip.

Funding

This study was funded by Tianjin Key Medical Discipline(Specialty) Construction Project.
Grants Awards No. TJYXZDXK-009 A.
This study was supported by the National Natural Science Foundation of China. Grants Awards No. 81872487 (to Liang Liu).

Data availability

Data is provided within the manuscript or supplementary information files.

Declarations

Human ethics and consent to participate

This study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethical Institution Tianjin Medical University Cancer Committee and Hospital (approval number: E20210961, date: 2021-11-26). Informed consent was obtained from all individual participants included in the study. The consent process was documented through written consent forms, and participants were ensured about the confidentiality of their data.

Consent for publication

Not Applicable.

Competing interests

The authors declare no competing interests.

Clinical trial number

Not Applicable.

Author details

[1]Tianjin Medical University Cancer Institute & Hospital, National Clinical Research Center for Cancer, Tianjin, China
[2]Tianjin's Clinical Research Center for Cancer, Tianjin, China
[3]Key Laboratory of Cancer Prevention and Therapy, Tianjin, China
[4]Key Laboratory of Cancer Immunology and Biotherapy, Tianjin, China

[5]Department of Biotherapy, Tianjin Medical University Cancer Institute & Hospital, Tianjin, China
[6]Department of Immunology, Tianjin Medical University Cancer Institute & Hospital, Tianjin, China
[7]Department of Lung Cancer, Tianjin Medical University Cancer Institute and Hospital, Tianjin, China
[8]Department of Oncology, Jiujiang No.1 People's Hospital, Jiujiang, Jiangxi, China

Received: 8 August 2024 / Accepted: 22 October 2024
Published online: 29 October 2024

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71:209–49.
2. Herbst RS, Heymach JV, Lippman SM. Lung cancer. N Engl J Med. 2008;359:1367–80.
3. Griesinger F, Korol EE, Kayaniyil S, Varol N, Ebner T, Goring SM. Efficacy and safety of first-line carboplatin-versus cisplatin-based chemotherapy for non-small cell lung cancer: a meta-analysis. Lung Cancer. 2019;135:196–204.
4. Rossi A, Di Maio M. Platinum-based chemotherapy in advanced non-small-cell lung cancer: optimal number of treatment cycles. Expert Rev Anticancer Ther. 2016;16:653–60.
5. Masters GA, Johnson DH, Temin S. Systemic therapy for stage IV non-small-cell lung cancer: American Society of Clinical Oncology Clinical Practice guideline update. J Oncol Pract. 2016;12:90–3.
6. Planchard D, Popat S, Kerr K, Novello S, Smit EF, Faivre-Finn C, et al. Metastatic non-small cell lung cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2018;29:iv192–237.
7. Batra U, Biswas B, Prabhash K, Krishna MV. Differential clinicopathological features, treatments and outcomes in patients with Exon 19 deletion and Exon 21 L858R EGFR mutation-positive adenocarcinoma non-small-cell lung cancer. BMJ Open Respir Res. 2023;10:e001492.
8. Recondo G, Facchinetti F, Olaussen KA, Besse B, Friboulet L. Making the first move in EGFR-driven or ALK-driven NSCLC: first-generation or next-generation TKI? Nat Rev Clin Oncol. 2018;15:694–708.
9. Maemondo M, Inoue A, Kobayashi K, Sugawara S, Oizumi S, Isobe H, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. N Engl J Med. 2010;362:2380–8.
10. Rosell R, Carcereny E, Gervais R, Vergnenegre A, Massuti B, Felip E, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol. 2012;13:239–46.
11. Wu YL, Zhou C, Hu CP, Feng J, Lu S, Huang Y, et al. Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-Lung 6): an open-label, randomised phase 3 trial. Lancet Oncol. 2014;15:213–22.
12. Leonetti A, Sharma S, Minari R, Perego P, Giovannetti E, Tiseo M. Resistance mechanisms to osimertinib in EGFR-mutated non-small cell lung cancer. Br J Cancer. 2019;121:725–37.
13. Yoneda K, Imanishi N, Ichiki Y, Tanaka F. Treatment of non-small cell Lung Cancer with EGFR-mutations. J UOEH. 2019;41:153–63.
14. Hosomi Y, Morita S, Sugawara S, Kato T, Fukuhara T, Gemma A, et al. Gefitinib alone versus gefitinib plus chemotherapy for non-small-cell lung cancer with mutated epidermal growth factor receptor: NEJ009 study. J Clin Oncol. 2020;38:115–23.
15. Saito H, Fukuhara T, Furuya N, Watanabe K, Sugawara S, Iwasawa S, et al. Erlotinib plus bevacizumab versus erlotinib alone in patients with EGFR-positive advanced non-squamous non-small-cell lung cancer (NEJ026): interim analysis of an open-label, randomised, multicentre, phase 3 trial. Lancet Oncol. 2019;20:625–35.
16. Zhang L, Wang L, Wang J, Chen J, Meng Z, Liu Z, et al. Anlotinib plus icotinib as a potential treatment option for EGFR-mutated advanced non-squamous non-small cell lung cancer with concurrent mutations: final analysis of the prospective phase 2, multicenter ALTER-L004 study. Mol Cancer. 2023;22:124.
17. Liu SY, Bao H, Wang Q, Mao WM, Chen Y, Tong X, et al. Genomic signatures define three subtypes of EGFR-mutant stage II-III non-small-cell lung cancer with distinct adjuvant therapy outcomes. Nat Commun. 2021;12:6450.
18. Liu Y, Xu F, Wang Y, Wu Q, Wang B, Yao Y, et al. Mutations in exon 8 of *TP53* are associated with shorter survival in patients with advanced lung cancer. Oncol Lett. 2019;18:3159–69.
19. Li XM, Li WF, Lin JT, et al. Predictive and prognostic potential of TP53 in patients with advanced non-small-cell lung cancer treated with EGFR-TKI: analysis of a phase III randomized clinical trial (CTONG 0901). Clin Lung Cancer. 2021;22(2):100–9.
20. Aggarwal C, Davis CW, Mick R et al. Influence of TP53 mutation on survival in patients with advanced EGFR-mutant non-small-cell lung cancer. JCO Precis Oncol. 2018;2018:PO.18.00107.
21. Canale M, Petracci E, Delmonte A, Chiadini E, Dazzi C, Papi M, et al. Impact of *TP53* mutations on outcome in *EGFR*-mutated patients treated with first-line tyrosine kinase inhibitors. Clin Cancer Res. 2017;23:2195–202.
22. Poeta ML, Manola J, Goldwasser MA, Forastiere A, Benoit N, Califano JA, et al. TP53 mutations and survival in squamous-cell carcinoma of the head and neck. N Engl J Med. 2007;357:2552–61.
23. Kurata T, Nakaya A, Yokoi T, Niki M, Kibata K, Takeyasu Y, et al. Phase I/II study of erlotinib, carboplatin, pemetrexed, and bevacizumab in chemotherapy-naïve patients with advanced non-squamous non-small cell lung cancer harboring epidermal growth factor receptor mutation. Genes Cancer. 2017;8:559–65.
24. Tamiya M, Tamiya A, Shiroyama T, Takeoka S, Naito Y, Omachi N, et al. Phase1 study of cisplatin plus pemetrexed with erlotinib and bevacizumab for chemotherapy-naïve advanced non-squamous non-small cell lung cancer with EGFR mutations. Invest New Drugs. 2018;36:608–14.
25. Rawluk J, Waller CF. Gefitinib. Recent Results Cancer Res. 2018;211:235–46.
26. Zhang Z, Zeng K, Zhao S, Zhao Y, Hou X, Luo F, et al. Pemetrexed/carboplatin plus gefitinib as a first-line treatment for EGFR-mutant advanced non small cell lung cancer: a Bayesian network meta-analysis. Ther Adv Med Oncol. 2019;11:1758835919891652.
27. Miyauchi E, Morita S, Nakamura A, Hosomi Y, Watanabe K, Ikeda S, et al. Updated analysis of NEJ009: gefitinib-alone versus gefitinib plus chemotherapy for non-small-cell lung cancer with mutated *EGFR*. J Clin Oncol. 2022;40:3587–92.
28. Cheng Y, Murakami H, Yang PC, He J, Nakagawa K, Kang JH, et al. Randomized phase II trial of gefitinib with and without pemetrexed as first-line therapy in patients with advanced nonsquamous non-small-cell lung cancer with activating epidermal growth factor receptor mutations. J Clin Oncol. 2016;34:3258–66.
29. Noronha V, Patil VM, Joshi A, Menon N, Chougule A, Mahajan A, et al. Gefitinib versus gefitinib plus pemetrexed and carboplatin chemotherapy in *EGFR*-mutated lung cancer. J Clin Oncol. 2020;38:124–36.
30. Garcia J, Hurwitz HI, Sandler AB, Miles D, Coleman RL, Deurloo R, et al. Bevacizumab (Avastin®) in cancer treatment: a review of 15 years of clinical experience and future outlook. Cancer Treat Rev. 2020;86:102017.
31. Stinchcombe TE. The use of EGFR tyrosine kinase inhibitors in EGFR wild-type non-small-cell lung cancer. Curr Treat Options Oncol. 2016;17:18.
32. Li A, Cao W, Liu X, Zhang Y, Ma Y, Xu R, et al. Gefitinib sensitization of cisplatin-resistant wild-type EGFR non-small cell lung cancer cells. J Cancer Res Clin Oncol. 2020;146:1737–49.
33. Gerlinger M, Rowan AJ, Horswell S, Math M, Larkin J, Endesfelder D, et al. Intratumor heterogeneity and branched evolution revealed by multiregion sequencing. N Engl J Med. 2012;366:883–92.
34. Chen ZY, Zhong WZ, Zhang XC, Su J, Yang XN, Chen ZH, et al. EGFR mutation heterogeneity and the mixed response to EGFR tyrosine kinase inhibitors of lung adenocarcinomas. Oncologist. 2012;17:978–85.
35. Mok TS, Wu Y-L, Ahn M-J, Garassino MC, Kim HR, Ramalingam SS, et al. Osimertinib or platinum-pemetrexed in EGFR T790M-positive lung cancer. N Engl J Med. 2017;376:629–40.

Publisher's note