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ORIGINAL RESEARCH

Bevacizumab Combined with Continuation of *EGFR*-TKIs in NSCLC Beyond Gradual Progression

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Objective: Continuation of epidermal growth factor receptor (*EGFR*)-tyrosine kinase inhibitors (TKIs) has shown potential in prolonging survival in patients with non-small cell lung cancer (NSCLC) harboring *EGFR* mutation who had gradual progression at initial targeting therapy. However, it remains unknown whether the combination of bevacizumab and continuation of *EGFR*-TKIs would benefit this subpopulation. This study retrospectively explored the effect of bevacizumab combined with *EGFR*-TKIs in NSCLC beyond gradual progression in the real-world setting.

Methods: The records of 48 patients were reviewed who received bevacizumab and continuation of *EGFR*-TKIs beyond gradual progression at initial targeting therapy. The response to the treatment and post progression survival (PPS) were reviewed and analyzed.

Results: The median PPS was 11.4 months (95% CI 7.368–15.492) for all patients included at the median follow-up time of 17.3 months. The objective response rate (ORR) was 8.3%, and the disease control rate (DCR) was 86.1% (with 3 partial response and 28 stable disease) in 36 patients who were evaluable for response with at least one measurable lesion. Univariate Cox analysis showed that age <60, male sex, and *EGFR* exon19 deletion mutation were associated with longer PPS ($P<0.05$). Patients harboring *EGFR* exon19 deletion mutation had significantly longer PPS than those with *EGFR* exon21 L858R mutation, with an mPPS of 15.5 months and 5.7 months, respectively (HR=0.251, 95% CI 0.112–0.561, $P=0.019$). Multivariate Cox analysis indicated that age <60 and *EGFR* exon19 deletion mutation were associated with longer PPS ($P<0.05$).

Conclusion: Continuation of *EGFR*-TKI with the combination of bevacizumab is a reasonable strategy in NSCLC patients beyond gradual progression in previous *EGFR*-TKI treatment. Younger patients with *EGFR* exon19 deletion mutation may benefit more from the combination therapy.

Keywords: *EGFR*-TKI, bevacizumab, NSCLC, gradual progression, combination therapy

Background

The application of epidermal growth factor receptor (*EGFR*)-tyrosine kinase inhibitors (TKIs) has greatly influenced the treatment of non-small-cell lung cancer (NSCLC) with activating *EGFR* mutations such as *EGFR* exon19 deletion and *EGFR* exon21 L858R mutation.[1,2] However, the resistance of *EGFR*-TKIs has been inevitable in the majority of NSCLC patients with *EGFR* mutation. Scientists have suggested that acquired resistance should meet the following criteria: objective clinical benefit from treatment with an *EGFR*-TKI as defined by either partial or complete response, or significant and durable stable disease of at least six months with an *EGFR*-TKI.[3] Underlying mechanisms of resistance have been proved complicated, including the T790M substitution,[4] *MET* amplification,[5] transformation to small-cell lung cancer, mutations in *PI3KCA* gene,[6] etc. Therefore, the clinical strategy is well worth exploring in *EGFR*-mutated NSCLC patients treated with *EGFR*-TKIs beyond progressive disease. Chinese scholars have established a clinical mode including three failure modes, namely dramatic progression, gradual progression, and local progression, aiming to favor subsequent strategies and predict survival benefit based on the previous definition of acquired resistance.

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Discontinuation of *EGFR*-TKI may accelerate disease progression for patients with gradual progression,[7] which was clinically defined as disease control lasting for at least six months and with progression in no more than two non-targeted lesions, and with the asymptomatic status or stability of pre-existing symptoms.[7] Continuation of *EGFR*-TKI could be an optional treatment strategy for subsequent therapy after failure, and obtained a longer overall survival (OS) than chemotherapy in this cohort (39.4 months vs 17.8 months, P=0.02).[8] A retrospective study in Japan also indicated that the continuation of *EGFR*-TKI beyond progressive disease (PD) may prolong OS compared with switching to chemotherapy (32.2 months vs 23.0 months, P=0.005).[9] However, it remains unknown whether the combination of *EGFR*-TKI and chemotherapy or other anti-tumor regimen would bring further benefit to *EGFR*-mutated NSCLC patients failed in *EGFR*-TKI treatment. Results in the IMPRESS trial have shown that continuation of gefitinib does not prolong progression-free survival (PFS) or OS in patients who received chemotherapy as subsequent therapy after PD on first-line gefitinib.[10,11] Few studies have explored the combination of *EGFR*-TKI and anti-angiogenic targeted agents such as bevacizumab and anlotinib after PD on previous *EGFR*-TKI treatment, especially for second- and third-generation *EGFR*-TKIs.[12,13] Anti-angiogenesis is potential in anti-tumor therapy as angiogenesis is another important process in the micro-environment related to tumor growth. Vascular endothelial growth factor (VEGF) binds to VEGF receptor (VEGFR)-2 and promotes tumor growth and progress by intriguing angiogenesis. Bevacizumab is a recombinant monoclonal VEGF-targeted agent that has been proved to prolong survival in advanced NSCLC patients when combined with chemotherapy.[14,15] Bevacizumab is widely used in various stages of lung cancer, which is also under study in combination with other anti-tumor agents, although the adverse events (AEs) such as hypertension and hemorrhage may lead to the discontinuation of treatment and will potentially be enhanced when combined with other anti-tumor agents. Preclinical studies have shown evidence that VEGF inhibitors may work synergistically with *EGFR*-TKIs[16] since *EGFR* influences VEGF signaling,[17] therefore the potent strategy of combining *EGFR*-TKIs and VEGF inhibitors might enhance the clinical efficacy in these patients. Clinical trials have demonstrated that using *EGFR*-TKI together with bevacizumab may prolong PFS compared to *EGFR*-TKI monotherapy as first-line treatment in *EGFR*-mutated NSCLC patients, although no significant difference was shown in long-term survival.[18,19] Furthermore, bevacizumab has played an essential role in improving the OS beyond initial PD for metastatic colorectal cancer patients.[20]

In this study, we explored the efficacy of combining bevacizumab and continuation of *EGFR*-TKI in NSCLC patients with gradual progression after *EGFR*-TKIs treatment to provide more evidence for an optimal clinical strategy in the real-world setting.

Methods

Patients

Patients who received combination of *EGFR*-TKI and bevacizumab beyond PD of previous *EGFR*-TKI treatment in the Chinese Academy of Medical Sciences (CAMS) during April 2018 to April 2021 were included in this retrospective study. The clinicopathological features have been collected from their medical records, including their gender, age, Eastern Cooperative Oncology Group performance status (ECOG-PS), smoking status, *EGFR* mutation status, and lines of *EGFR*-TKI therapy. The dates of *EGFR*-TKI initiation, bevacizumab initiation, and Response Evaluation Criteria of Solid Tumors (RECIST)-defined PD were also obtained.

This study was approved by the Ethics Committee of the National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, CAMS and Peking Union Medical College (approval No. 19–096-1881).

Treatment Strategy

All patients were treated with *EGFR*-TKIs, including first-generation *EGFR*-TKI erlotinib, gefitinib, icotinib, second-generation *EGFR*-TKI afatinib and dacomitinib, and third-generation osimertinib, which were all proved by National Medical Products Administration. When gradual progression occurred, these patients continued previous *EGFR*-TKI combined with bevacizumab as subsequent treatment, with or without local treatment such as radiotherapy. Tissue or liquid biopsy for further gene tests using next-generation sequencing (NGS) assay was suggested after progression. The patients

were excluded if they were suspended from therapy with bevacizumab due to tolerability or any other reason, and only those who had continuation of *EGFR*-TKI combined with bevacizumab until progression were included in this study.

Clinical Assessment

Gradual progression was considered to occur in patients with the disease control lasting for at least six months by using previous *EGFR*-TKI therapy, with progression in no more than two non-targeted lesions, and with the symptomatic status or stability of pre-existing symptoms according to previous studies. The assessment of efficacy of subsequent treatment was based on the RECIST version 1.1.[21] The indexes of efficacy assessment were evaluated by post progression survival (PPS), overall survival (OS), objective response rate (ORR), complete response (CR), partial response (PR), disease control rate (DCR), and stable disease (SD) rates. PPS was defined as the period between initial PD confirmation and either discontinuation of bevacizumab plus *EGFR*-TKI or death from any cause, and OS was defined as the period from the initiation of combination treatment to death from any cause or the last follow-up. ORR was defined as the sum of CR and PR rates, and DCR was defined as the sum of the CR, PR, and SD rates.

The relationship between PPS and clinicopathological characteristics was analyzed using univariate analysis and multivariate analysis, including age, gender, ECOG PS, tumor stage, brain metastases, best response to prior *EGFR*-TKI, type of disease progression lesion, treatment strategy, and line of targeted therapy. *EGFR* mutation status at diagnosis was also analyzed as a factor.

Statistical Analysis

Clinical characteristics and responses to therapy of patients were analyzed with descriptive statistics. Continuous variables were compared by *t*-tests, and categorial variables were analyzed by $\chi 2$ tests. All statistical analysis was performed by utilizing SPSS version 26.0, and P value <0.05 was considered significant. Median PPS was calculated by Kaplan–Meier product limit method. Risk factors for PPS were analyzed with the univariate Cox proportional hazards regression model and the multivariate analysis by using a Cox proportional hazards model, using the following covariates: age, gender, ECOG PS, tumor stage, brain metastases, best response to prior EGFR-TKI, type of disease progression lesion, treatment strategy, line of targeted therapy, and *EGFR* mutation status at diagnosis.

Results

Characteristics of Patients and Treatments

Until 28th July 2021, the median time of follow-up was 17.3 months. Totally 48 patients were incorporated into this retrospective study, including 19 patients (39.5%) who received first-generation *EGFR*-TKIs, 14 patients (29.2%) who received second-generation *EGFR*-TKIs, and 15 patients (31.3%) who received third-generation *EGFR*-TKI. All patients continued previous *EGFR* targeted treatment with the addition of bevacizumab when gradual progression occurred, assessed by investigators. The majority of patients were female who never smoked with a good ECOG-PS, with a median age 57 (range 33–74) (Table 1). All patients had an *EGFR* mutation, and the exon19 deletions and L585R point mutations covered about 87.6% of this cohort. The median time on initial *EGFR*-TKI was 13.1 months (range 6.0–62.1 months). *EGFR*-TKIs had been given in the first-line setting for 64.6% of patients (Table 1).

The Assessment of Clinical Efficacy

A total of 36 patients were evaluable for response with at least one measurable lesion (Table 2). The PR, SD, ORR, and DCR were observed in 8.3% (3/36), 77.8% (28/36), 8.3% (3/36), and 86.1% (31/36) of patients, respectively. Progression occurred in 13.8% of patients (5/36) at first evaluation, and totally 33 of 48 patients (68.8%) had PD until last follow-up on 28th July 2021, and 11 patients (22.9%) had died. Median PPS for all patients included was 11.4 months (95% CI 7.368–15.492), as shown in Figure 1. Overall survival was immature at the time of data cutoff.

In 22 patients out of 33 (66.7%) who progressed beyond first- or second-generation *EGFR*-TKIs combining bevacizumab, 4 patients had died of dramatic progression and thus had not received further gene tests. Among 18

Table 1 Clinicopathological Features of All NSCLC Patients Harboring *EGFR*-Activating Mutations Who Received *EGFR*-TKIs Combined with Bevacizumab Beyond Gradual Progression of *EGFR*-TKIs as Subsequent Therapy

Characteristics	***n***	%
Age		
Median	57	
Range	33–74	
Sex		
Male	16	33.3
Female	32	66.7
Smoking status		
Never	38	79.2
Current/former	10	20.8
ECOG PS		
≤1	44	91.7
>1	4	8.3
Brain metastasis prior to *EGFR*-TKIs		
Present	22	45.8
Absent	26	54.2
Brain radiotherapy		
Yes	12	25.0
No	10	20.8
No brain metastases	26	54.2
Tumor stage		
IV	32	66.7
Postoperative recurrence	16	33.3
Type of disease-progression lesion		
Previously evaluated	32	66.7
New metastatic	16	33.3
Line of targeted therapy		
1	31	64.6
2	10	20.8
≥3	7	14.6
Time on initial *EGFR*-TKIs		
Median	6.0–62.1 months	
Range	13.1 months	
Best response to prior *EGFR*-TKIs		
CR/PR	17	35.4
SD/PD	22	45.8
No measurable lesions	9	18.8
EGFR mutation at diagnosis		
Exon19 deletion	27	56.3
Exon21 mutation (L858R)	15	31.3
Other *EGFR* mutation	6	12.4
Treatment strategy		
First-generation *EGFR*-TKI+bevacizumab	19	39.5
Second-generation *EGFR*-TKI+bevacizumab	14	29.2
Third-generation *EGFR*-TKI+bevacizumab	15	31.3

Abbreviations: *n*, number; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitors; RT, radiotherapy.

Table 2 Treatment Outcomes of Combining Bevacizumab and *EGFR*-TKIs Beyond Progressive Disease in 36 NSCLC Patients Harboring *EGFR*-Activating Mutations with at Least One Measurable Lesion

Overall Best Response	*n* (%)
CR	0 (0)
PR	3 (8.3)
SD	28 (77.8)
PD	5 (13.9)
ORR	3 (8.3)
DCR	31 (86.1)

Abbreviations: *n*, number; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate (ORR=CR+PR); DCR, disease control rate (DCR=CR+PR+SD).

patients who underwent a liquid biopsy for NGS testing, 12 patients (66.7%) had T790M-positive status, while the other 6 patients (33.3%) had no acquired T790M mutation.

The Exploration of Risk Factors

The univariate Cox proportional hazards regression model indicated that female patients had significantly shorter PPS than male patients, with an mPPS of 8.4 months and 20.8 months, respectively (HR=2.726, 95% CI 1.176–6.319, *P*=0.019), as shown in Figure 2. Younger patients (<60 years old) had significantly longer PPS than older patients (≥60

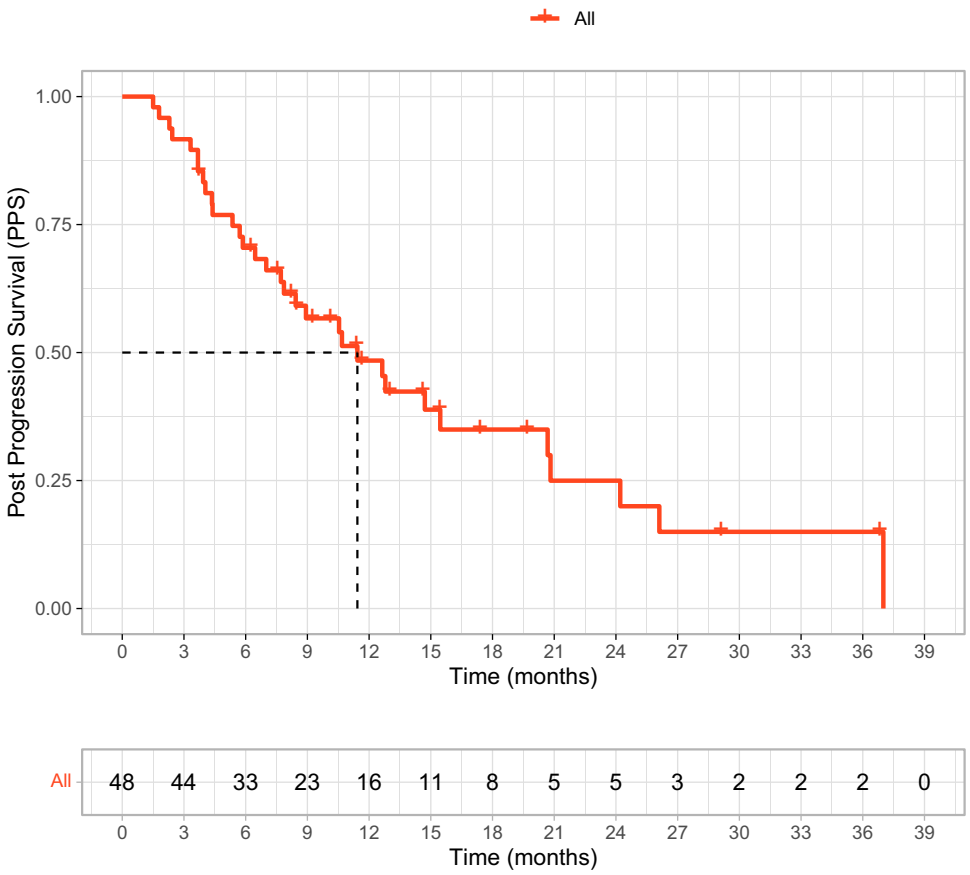

Figure 1 Kaplan–Meier curves of post progression survival (PPS) for the entire population.

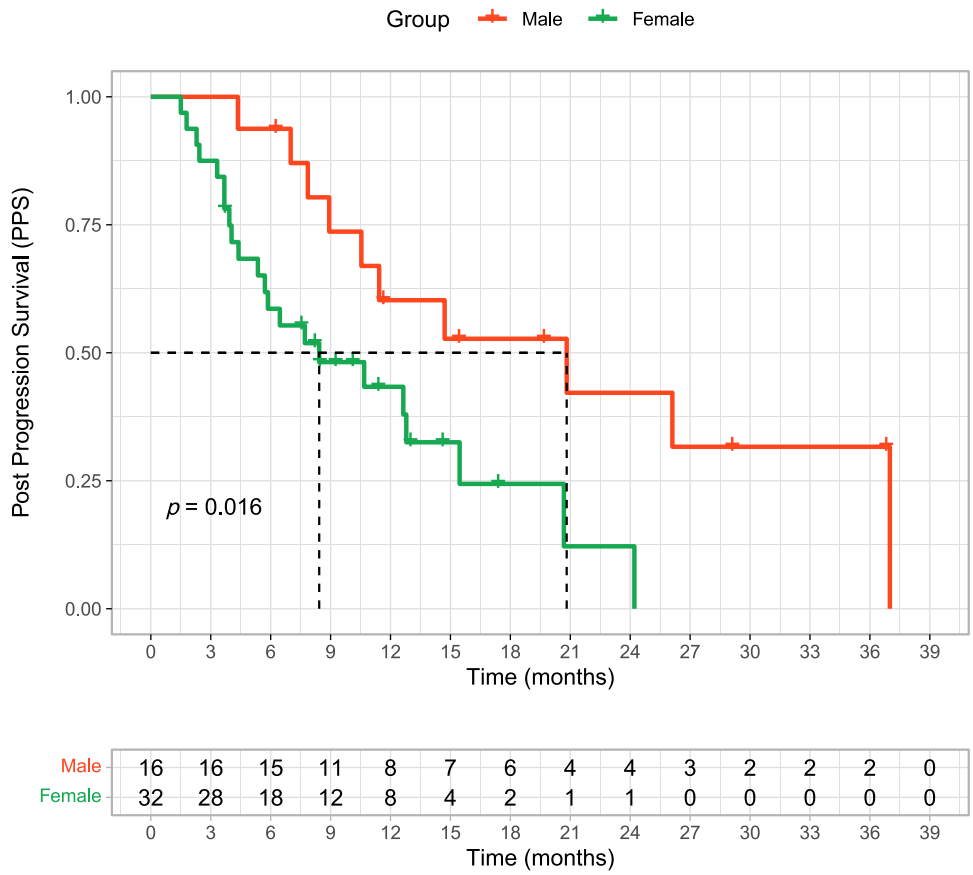

Figure 2 Post progression survival (PPS) curves of male and female advanced non-small-cell lung cancer patients who received combination of bevacizumab and continuation of epidermal growth factor receptor (*EGFR*)-tyrosine kinase inhibitors (TKIs) beyond gradual progression.

years old), with an mPPS of 14.7 months and 7.0 months, respectively (HR=0.485, 95% CI 0.237–0.990, *P*=0.047), as shown in Figure 3. Patients who had recurrence after operation had numerically longer PPS than those who were diagnosed at stage IV (24.2 months vs 10.5 months); however, no significant difference has been observed (*P*=0.160). Patients harboring *EGFR* exon21 L858R mutation had significantly shorter PPS than those with *EGFR* exon19 deletion mutation, with an mPPS of 5.7 months and 15.5 months, respectively (HR=4.003, 95% CI 1.810–8.855, *P*<0.01) (Figure 4). No significant difference has been observed in PPS in patients with and without brain metastases before combination treatment (10.5 vs 11.4 months, *P*=0.896), and PPS did not differ in patients with brain metastases who received brain radiotherapy and those who did not (10.5 vs 7.9 months, *P*=0.424). The results for univariate Cox analyses are displayed in Figure 5. A multivariate analysis of prognostic factors was further performed by using a Cox proportional hazards model (Figure 6). Results showed that *EGFR* exon19 deletion mutation was an independent prognostic factor in PPS (*P*=0.003). Younger patients (<60 years old) had significantly a lower risk of disease progression or death than older patients (≥60 years old), indicating that age was also an independent prognostic factor in PPS (*P*=0.003).

Discussion

EGFR-TKIs are the standard treatment for NSCLC patients harboring activating *EGFR* mutations.[22] However, the majority of patients develop acquired resistance with the eventual appearance of PD, usually assessed by RECIST. This criterion, though widely used, does not comprehensively reflect the diversity of *EGFR*-TKI failure, which might cause the discontinuation of *EGFR*-TKIs. Previous studies have demonstrated that the duration of disease control, evaluation of tumor burden by documentations of target and non-target lesions, and clinical symptoms are closely correlated to prognosis.[8] Therefore, it is reasonable to further categorize *EGFR*-TKI failure modes based on the factors

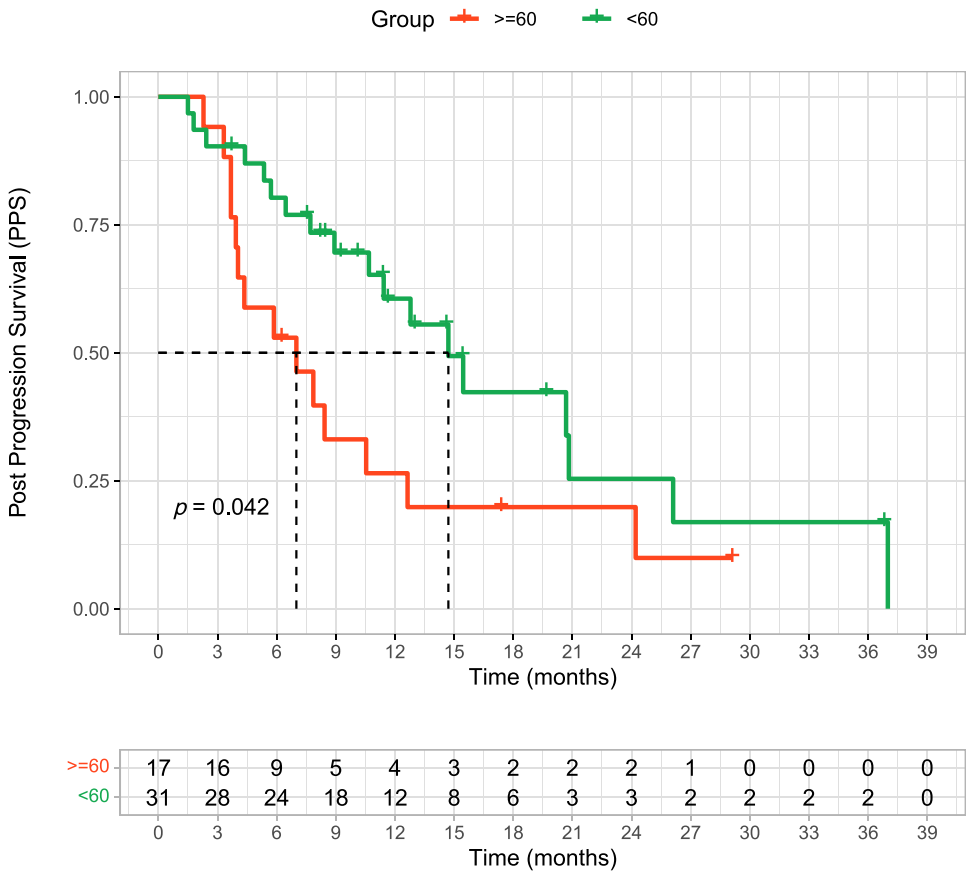

Figure 3 Post progression survival (PPS) curves of younger and older advanced non-small-cell lung cancer patients who received combination of bevacizumab and continuation of epidermal growth factor receptor *(EGFR)*-tyrosine kinase inhibitors (TKIs) beyond gradual progression.

mentioned above, and to make a clinical decision on subsequent management according to more precise and personalized information. This retrospective study focused on the combination strategy of *EGFR*-TKI and bevacizumab in *EGFR*-mutated NSCLC patients who had gradual progression in previous *EGFR*-TKI treatment. Compared to historical data of continuation of *EGFR*-TKI beyond gradual progression, with a median duration time of 3.2 to 5.4 months,[10,23] our results showed that this combination strategy could be an option for patients who had gradual progression on *EGFR*-TKIs with a prolonged duration time, especially for younger (<60 years old) patients with *EGFR* exon19 deletion mutation.

It has been hypothesized that the combination strategy may delay the resistance of *EGFR*-TKIs, given that *EGFR*-TKIs may work synergically with chemotherapy or antiangiogenic agents. The efficacy has been explored in several clinical trials for combining platinum-based chemotherapy and *EGFR*-TKIs for NSCLC patients harboring *EGFR*-sensitive mutation,[24,25] suggesting that this combination regimen may obtain a longer PFS and OS than *EGFR*-TKI monotherapy as first-line treatment.[24,25] However, continuation of *EGFR*-TKI combined with chemotherapy has not improved clinical outcomes compared to chemotherapy alone in first-generation *EGFR*-TKI failures.[26] Therefore, continuation of *EGFR*-TKI was not recommended for patients who received platinum-based chemotherapy after *EGFR*-TKI progression.[10,11] A preclinical experiment established that bevacizumab suppressed tumor regrowth even in erlotinib-refractory phase to prolong the anti-tumor effect in mouse xenograft models.[27] The study found that complete tumor regression was observed in 2/7 mice treated with concurrent therapy of bevacizumab and erlotinib but not in erlotinib monotherapy,[27] while addition of bevacizumab still suppressed tumor regrowth in those that were erlotinib-refractory,[27] through comparing the anti-tumor activity by evaluating tumor volume (TV) with concurrent therapy and bevacizumab add-on treatment in erlotinib-refractory phase and defining complete tumor regression as a TV below detection limit <15 mm.[27] In clinical trials, the concurrent strategy of bevacizumab and first-generation *EGFR*-TKI has shown potential in achieving higher response and longer survival than *EGFR*-TKI alone.[28,29] However, the concurrent combination strategy has failed to prolong long-term

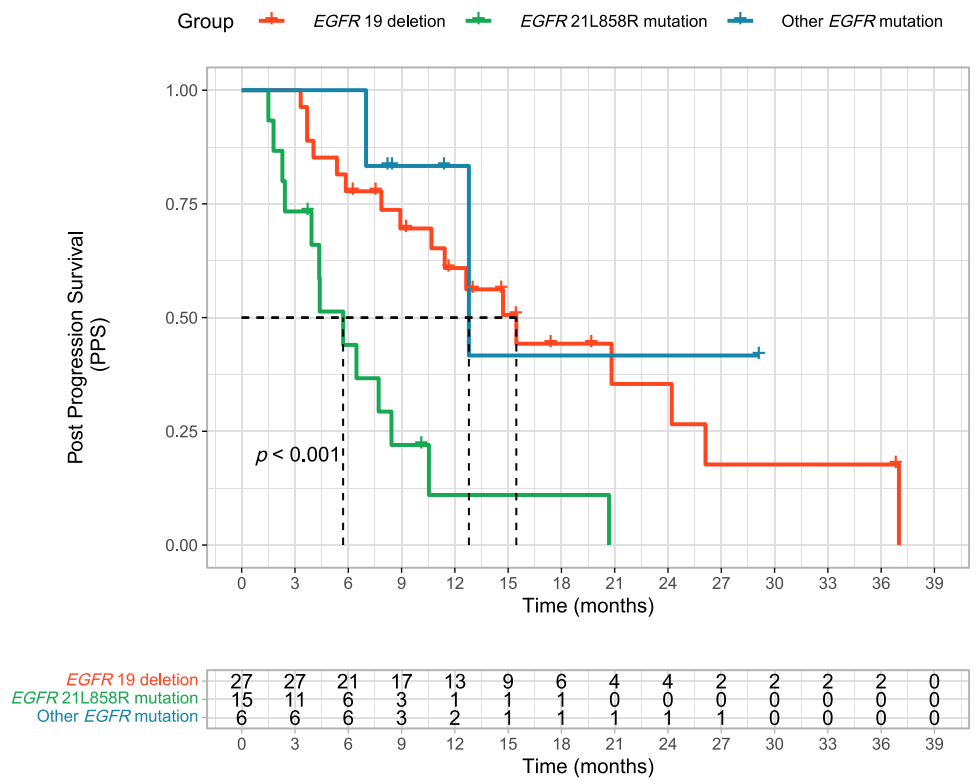

Figure 4 Post progression survival (PPS) curves of advanced non-small-cell lung cancer patients with different epidermal growth factor receptor (*EGFR*) mutation status who received combination of bevacizumab and continuation of *EGFR*-tyrosine kinase inhibitors (TKIs) beyond gradual progression.

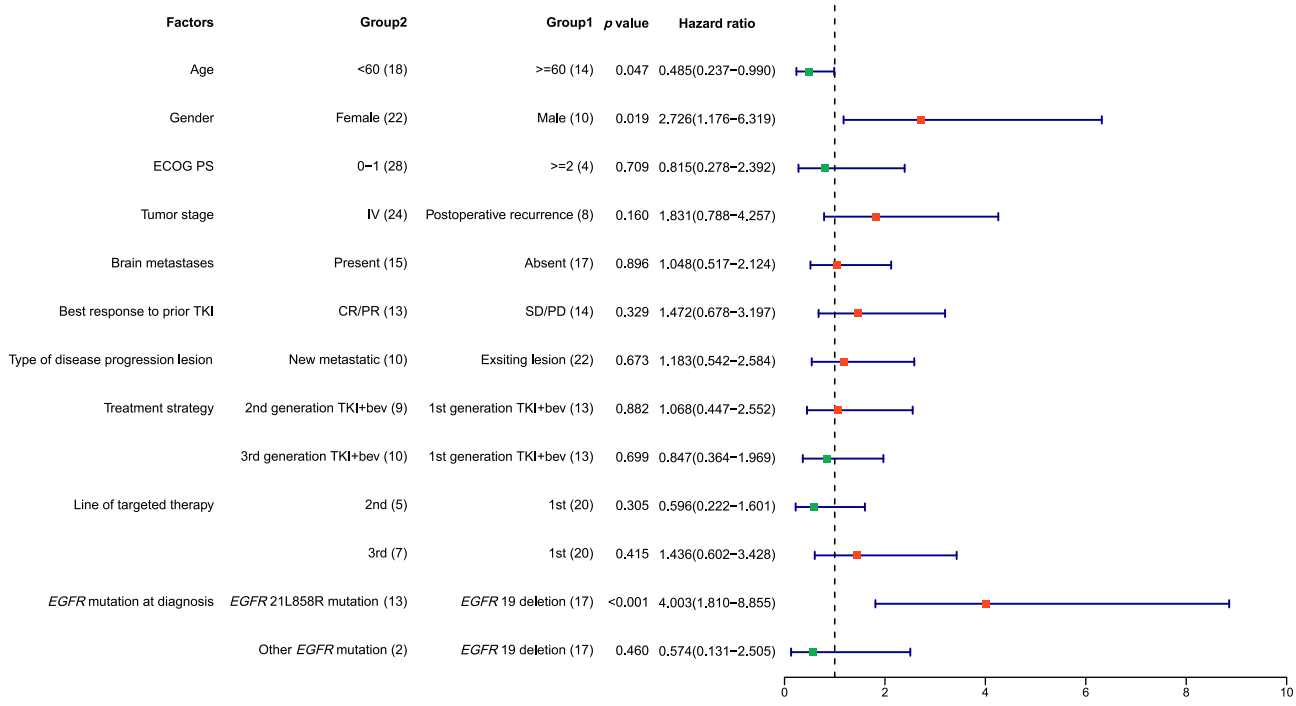

Figure 5 Hazard ratio of post progression survival (PPS) in patients with different characteristics using univariate analysis. A hazard ratio less than 1 implies a lower risk of disease progression or death in group 2 than in group 1. The number of cases that had progressive disease is shown in each group for every characteristic.

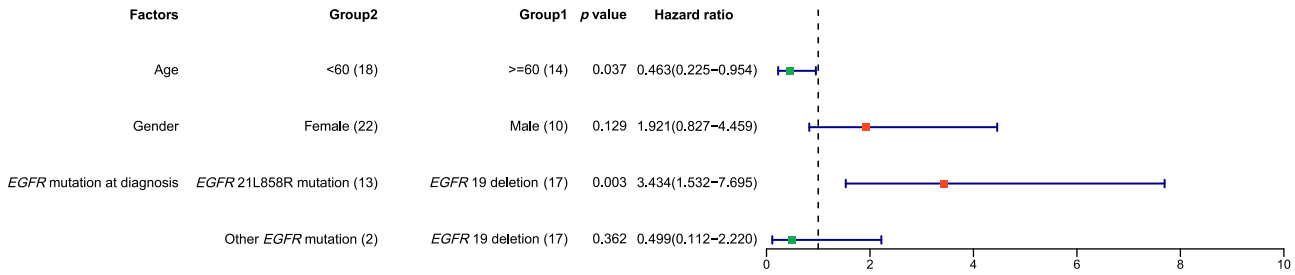

Figure 6 Hazard ratio of post progression survival (PPS) in patients with different characteristics using multivariate analysis. A hazard ratio less than 1 implies a lower risk of disease progression or death in group 2 than in group 1. The number of cases that had progressive disease is shown in each group for every characteristic.

survival, and has caused a higher rate of adverse events compared with monotherapy.[18,19] Moreover, little evidence has been given on whether the addition of bevacizumab would benefit patients who are *EGFR*-TKI-refractory, and thus the optimization of scheduling is still under investigation for this combination therapy. Evidence has also been scarce for combining bevacizumab and second- or third-generation *EGFR*-TKI beyond PD. Our study has analyzed the efficacy of bevacizumab combined with continuation of first-, second-, and third-generation *EGFR*-TKIs beyond gradual progression, and has observed a median PPS of 11.4 months with no significant difference among the three generations of *EGFR*-TKIs, indicating that this strategy may be beneficial to patients who had gradual progression after *EGFR*-TKIs of any generation.

The two representative *EGFR* mutations, *EGFR* exon19 deletion and *EGFR* exon21 L858R missense mutation, have led to constitutively activated *EGFR* kinase readily inhibited by *EGFR*-TKIs.[30] Subgroup analyses in large clinical trials have shown that the efficacy of *EGFR*-TKIs still varied in these two subpopulations of NSCLC patients.[31] The underlying mechanisms remained controversial regarding whether patients harboring *EGFR* exon19 deletion tended to have longer survival than those with *EGFR* exon21 mutations.[32] *EGFR* exon21 mutation is a Class II mutation and is a single-nucleotide substitution,[33] which is unlike *EGFR* exon19 deletion, a Class I mutation including short in-frame deletions that result in the loss of four to six amino acids.[33] For one thing, concomitant genetic alterations, such as *PIK3CA*, *AKT1*, and *ERBB2*, were correlated with reduced response to *EGFR*-TKI and poorer survival, and studies have indicated that patients with *EGFR* exon21 mutation had a significantly higher incidence of concomitant mutation somatic than those with *EGFR* exon19 deletion mutation.[34,35] Moreover, tumor mutation burden was shown to be negatively associated with clinical outcomes in *EGFR*-mutant NSCLC patients by treating with *EGFR*-TKI, which was higher in *EGFR* exon21 L858R patients than in those with *EGFR* exon19 deletion.[36] Previous studies have indicated that these two kinds of mutations should be considered distinct clinical entities due to their different response to *EGFR*-TKIs, therefore it is necessary to seek an optimal strategy for each subset of patients harboring *EGFR* mutations. Second-generation *EGFR*-TKI dacomitinib has shown efficacy in NSCLC patients harboring *EGFR* exon21 L858R, representing benefit in both PFS and OS.[37] However, the study has not proved whether the single agent will benefit patients with brain metastasis at diagnosis, and combination therapy of *EGFR*-TKI and bevacizumab seems to be a promising strategy for this subpopulation. In the subgroup study of trial CTONG1509, the PFS was 19.5 months for patients harboring L858R mutations treated by bevacizumab plus erlotinib, twice that by erlotinib monotherapy (9.7 months).[28] The HR for risk of PD in *EGFR* exon21 mutation and *EGFR* exon19 deletion was 0.51 and 0.62, respectively, indicating that patients harboring exon21 L858R mutations might benefit more from the combination therapy than those harboring exon19 deletion mutation.[28] Further evidence is still required to determine the optimal strategy for *EGFR* exon21 L858R mutation. Results suggested that *EGFR* mutation status could be an independent factor for survival even beyond progression, with a longer PPS in patients harboring *EGFR* exon19 deletion than those with *EGFR* exon21 L858R point mutation (P=0.001) in this study. Previous studies have indicated that *EGFR*-T790M mutation accounts for approximately 50% of acquired resistance to first- or second-generation *EGFR*-TKIs.[4] Our study reported a relatively higher rate of T790M occurrence (66.7%) after progression of combining bevacizumab and *EGFR*-TKI. However, a future study of larger sample size is still needed to further explore the mechanisms of acquired resistance.

Brain metastasis is one of the leading causes of lung cancer mortality, and brain tumors are often surrounded by brain edema that perhaps causes neurological symptoms and affects the quality of life. Treatment strategies are limited, including surgery and radiotherapy, which would also cause permanent damage to brain. Preclinical data suggested that bevacizumab

prevented brain metastasis formation and prolonged the survival in a NSCLC mouse model,[38] possibly via inhibiting the endothelial cell.[38] Evidence has been also shown that bevacizumab relieved the clinical symptoms and reduced the edema volumes in brain metastatic patients by blocking the binding of VEGF-A to its receptors.[39] A phase II trial has demonstrated the efficacy of bevacizumab plus paclitaxel and carboplatin as first-line treatment in NSCLC patients with asymptomatic,[40] untreated brain metastases, with the mPFS, mOS, and ORR of 6.7 months, 16.0 months, and 62.7%, respectively.[40] *EGFR*-TKIs may be favorable options which lowered the incidence of intracranial progression,[41,42] since chemotherapy had trouble in crossing the blood–brain barrier and acting on micrometastatic brain lesions.[41,42] A phase I/II study has explored the safety and efficacy of combining osimertinib and bevacizumab as initial treatment for NSCLC patients, in whom 31% of patients diagnosed with brain metastases were enrolled. The ORR was 100% for six patients with measurable brain lesions, compared to 66% in the FLAURA study, indicating the intracranial efficacy of combination therapy.[12] A phase II study has further researched the efficacy of osimertinib and bevacizumab as subsequent therapy in NSCLC patients with *EGFR* T790M mutation after prior *EGFR*-TKI treatment.[13] The result of this phase II study, however, has failed to identify the advantage of bevacizumab and osimertinib in patients with brain metastases, due to the small sample size of this subgroup.[13] In our study, no significant difference has been observed in patients with or without brain metastases prior to combination therapy of *EGFR*-TKI and bevacizumab beyond gradual progress (P=0.896), and the addition of brain radiotherapy has not prolonged the PPS of those patients with brain metastases (P=0.421). This result is parallel to previous studies,[13] which may also be due to the limitation of sample size. Notably, three patients have partial response to the continuation of *EGFR*-TKI plus bevacizumab in our study, including a complete intracranial response in one patient, despite the evidence that had been suggested by previous preclinical experiment.[27]

There are several limitations in this study. As a single-arm retrospective study, the sample is not large enough especially for subgroup analysis, therefore, it has failed to compare the efficacy of bevacizumab combined with continuation of *EGFR*-TKIs to other anti-tumor strategies in the control group. Studies with larger samples and multiple cohorts in multi-centers or meta-analyses are needed to further verify the conclusion. Moreover, data for OS have been immature until last follow-up, therefore the relationship between the treatment duration of bevacizumab beyond progression and OS should be explored in future studies.

Conclusion

This study has provided evidence that continuation of *EGFR*-TKI with the combination of bevacizumab is a reasonable strategy in NSCLC patients beyond gradual progression in previous *EGFR*-TKI treatment. Younger patients with *EGFR* exon19 deletion mutation may benefit more from the combination therapy.

Abbreviations

EGFR-TKIs, epidermal growth factor receptor-tyrosine kinase inhibitors; NSCLC, non-small cell lung cancer; PPS, post progression survival; ORR, objective response rate; DCR, disease control rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor; CAMS, Chinese Academy of Medical Sciences; ECOG-PS, Eastern Cooperative Oncology Group performance status; RECIST, Response Evaluation Criteria of Solid Tumors; CR, complete response; PR, partial response; SD, stable disease; COX, Cox proportional hazards regression model; TV, tumor volume.

Data Sharing Statement

Data are available on request to our corresponding authors via e-mail address provided in the title page.

Ethics Committee Approval and Patient Consent

The present study was approved by the ethics committee of Cancer Hospital, CAMS and Peking Union Medical College (approval No. 19-096-1881). Informed consent was waived by the ethics committee due to the retrospective nature of review. The data were maintained with confidentiality, and this study was performed in compliance with the Declaration of Helsinki.

Consent for Publication

All authors consent to publication.

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Disclosure

The authors have no competing interests.

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