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Original Research

EGFR-TKIs plus bevacizumab demonstrated survival benefit than EGFR-TKIs alone in patients with EGFR-mutant NSCLC and multiple brain metastases☆

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KEYWORDS
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Abstract ***Introduction:*** Previous studies suggested that epidermal growth factor receptor (EGFR)–tyrosine kinase inhibitor (TKIs) plus bevacizumab could significantly prolong progression-free survival (PFS) than EGFR-TKI alone as first-line setting for patients with EGFR-mutant non-small-cell lung cancer (NSCLC). However, whether this combination could benefit patients with multiple brain metastases (BrMs) remains undetermined.
Methods: A total of 208 patients with EGFR-mutant NSCLC and multiple BrM (number >3, at least one of lesions was measurable) were retrospectively identified. Kaplan-Meier curves with two-sided log-rank tests and Cox proportional hazards model with calculated hazard ratios and 95% confidence intervals were used to determine the survival difference.
Results: Of all patients, 149 patients received EGFR-TKIs monotherapy and 59 received EGFR-TKIs plus bevacizumab as first-line setting. EGFR-TKIs plus bevacizumab was

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associated with a significantly higher intracranial objective response rate (ORR, 66.1% vs. 41.6%, $P = 0.001$), systemic ORR (74.6% vs. 57.1%, $P = 0.019$), longer intracranial PFS (14.0 vs. 8.2 months; $P < 0.001$) and systemic PFS (14.4 vs. 9.0 months; $P < 0.001$). Importantly, addition of bevacizumab also had a significantly longer overall survival (OS, 29.6 vs. 21.7 months; $P < 0.001$). Multivariate analysis consistently revealed that addition of bevacizumab was independently associated with prolonged intracranial and systemic PFS, and OS. No unexpected serious adverse effects were observed.

Conclusions: EGFR-TKIs plus bevacizumab prolonged not only PFS but also OS in patients with EGFR-mutant NSCLC and multiple BrMs when compared with EGFR-TKIs alone, indicating that this combination could be an alternative therapeutic option for those patients.

1. Introduction

Brain metastasis (BrM) is one of the most common distant metastases in patients with advanced non-small-cell lung cancer (NSCLC) [1]. It is still an intractable disease in those patients, together with an unsatisfactory prognosis [2]. The discovery of epidermal growth factor receptor (EGFR)–activating mutations has revolutionised the treatment landscape and results in the significant prolongation of progression-free survival (PFS) in patients with EGFR-mutant NSCLC [3–5]. Although third-generation epidermal growth factor receptor (EGFR)–tyrosine kinase inhibitors (TKIs) (e.g. osimertinib) with improved central nervous system (CNS) penetration and activity showed the superior CNS efficacy than first-generation EGFR-TKIs in patients with EGFR-mutant BrM [6,7], the limited therapeutic options beyond osimertinib suggested that alternative strategies are still urgently needed.

Vascular endothelial growth factor (VEGF) and its receptor (VEGFR) play a significant role in the angiogenesis and progression of NSCLC [8,9]. Preclinical studies suggested that simultaneous inhibition of the EGFR and VEGF/VEGFR pathways could yield a biologically synergistic effect on antitumour activity [10]. Naumov *et al.* [11] further found that simultaneous blockade of the VEGF/VEGFR and EGFR pathways could eliminate both primary resistance to EGFR-TKIs and/or acquired resistance due to the EGFR T790M mutation. Two recent clinical trials (JO25567 and NEJ026) corroborated this finding and found that EGFR-TKIs plus bevacizumab resulted in a significant prolongation of PFS than EGFR-TKIs alone in first-line setting for patients with advanced non-squamous EGFR-mutant NSCLC [12,13]. However, the updated analysis of JO25567 study showed that this combination failed to improve overall survival (OS), and the OS data in NEJ026 study are still immature [14].

Previously, several retrospective single-arm studies have reported the promising survival benefit (including OS) of EGFR-TKIs plus bevacizumab in patients with EGFR-mutant NSCLC and BrM [15,16]. As is known, JO25567 study did not include patients with BrM. Patients with asymptomatic CNS metastases were considered eligible to be enrolled in NEJ026 study. Subgroup analysis suggests that the addition of bevacizumab tends to have PFS benefit for patients with asymptomatic CNS metastases [hazard ratios (HRs): 0.78, 95% confidence intervals (CIs): 0.42–1.43] [13]. Therefore, whether EGFR-TKIs plus bevacizumab could benefit those patients with multiple BrMs remains undetermined. This multiple-centre retrospective study aimed to investigate the efficacy of EGFR-TKIs plus bevacizumab compared with EGFR-TKIs alone in patients with EGFR-mutant NSCLC and multiple BrMs.

2. Methods

2.1. Patients' inclusion

The main inclusion criteria were as follows: (1) histological or pathological confirmation of advanced non-squamous NSCLC, (2) American Joint Committee on Cancer (AJCC) 7th Edition or The International Association for the Study of Lung Cancer (IASLC) lung cancer 7th tumour-node-metastasis classification stage IV disease, (3) EGFR-activating mutations tested by amplification-refractory mutation system (ARMS), (4) radiological confirmation of multiple BrMs (number >3, at least one of the lesions was measurable) including cranial magnetic resonance imaging (MRI) and/or enhanced computed tomography (CT). The major exclusion criteria are as follows: (1) patients with leptomeningeal metastases, (2) previous cranial radiotherapy or surgery. Patients with symptomatic BrMs were eligible, but those with severe neurological symptoms including intracranial haemorrhage, uncontrollable intracranial hypertension or oedema were excluded. Other symptoms indicated testing included whole-body positron-emission tomography (PET) or PET/CT, abdominal CT, abdominal ultrasound and bone scan. The flow chart is seen in Fig. 1. The ethics committee

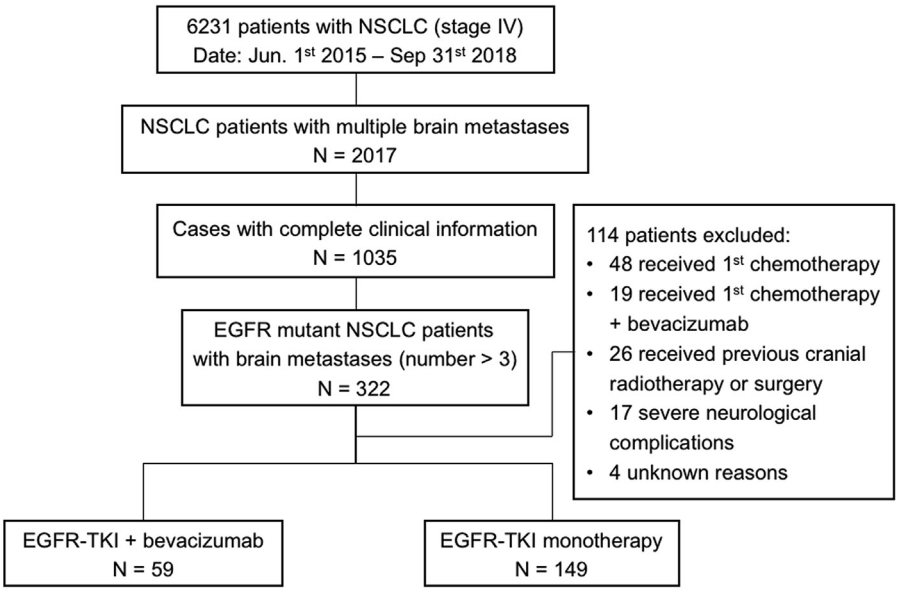

Fig. 1. Flow chart of patient selection. NSCLC, non-small-cell lung cancer.

and institutional review board of each centre approved the study protocol. Patients who met these criteria were identified in two Chinese medical centres with similar standard operation procedure for multiple BrMs from June 2015 to September 2018.

2.2. Data collection

Data from eligible patients were retrospectively collected from electronic medical records. The Thoracic Cancer Institute, Tongji University School of Medicine, set the requirements for clinical information on patient follow-up under treatment, including response to treatment and clinical outcomes. The major clinicopathological parameters including age, sex, smoking history, Eastern Cooperative Oncology Group performance status (ECOG PS), lung cancer histology (World Health Organisation classification) [17], nodal stage, number of BrMs, sites of extracranial metastasis, EGFR mutational status and types of EGFR-TKIs were collected. A never-smoker was defined as a person who had smoked <100 cigarettes during his/her lifetime. Smoking status, ECOG PS and age were recorded at the time of initial diagnosis. EGFR common mutations included exon 19 deletion (19DEL) and Leu858Arg point mutation in exon 21 (L858R). EGFR rare mutations were those mutations other than 19DEL and L858R. EGFR mutational status was tested at each medical centre. Briefly, DNA from tissue was extracted using the DNeasy Tissue Kit or the QIAamp DNA FFPE Tissue Kit (both from Qiagen, Hilden, Germany). EGFR mutations were determined by ARMS as described in our previous publications (Amoy Diagnostics Co. Ltd., Xiamen, China) [18–20]. The EGFR-TKIs used in this study included gefitinib (250 mg, once a day), erlotinib (150 mg, once a day) and icotinib (125 mg, three times a day). Bevacizumab (7.5 or 15 mg/kg) was used by intravenous infusion on day 1 of a 21-day cycle. Whether bevacizumab was added to EGFR-TKIs was left to the discretion of investigators or patients. Intracranial tumour response (by MRI) and extracranial tumour response (by CT), including complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD), were assessed every 6–8 weeks according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. The treatment response was evaluated one month after the initiation of therapy and then every two months. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTC-AE), version 4.0.

2.3. Statistical analysis

The difference of baseline features between different treatment groups was compared using the χ^2 test. The categorical variables were compared using the chi-square test or Fisher exact test when needed. The continuous variables were analysed using the analysis of variance (ANOVA) and Tukey multiple comparison tests. Intracranial PFS (iPFS) was defined as the time from the date of initiation of first-line setting to the date of intracranial progression or death and was censored at the date of the last tumour assessment (when carried out). Systemic PFS (sPFS) was defined as the time from the date of initiation of first-line setting to the date of systemic progression (except intracranial progression) or death and was censored at the date of the last tumour assessment (when carried out). Kaplan-Meier curves with two-sided log-rank tests and Cox proportional hazards model with calculated HRs and 95% CIs were used to determine the

survival difference. Two-sided $P < 0.05$ was considered statistically significant. All statistical analyses were performed using the SPSS statistical software, version 20.0, (SPSS Inc., Chicago, IL, USA).

3. Results

A total of 2017 patients with NSCLC and multiple BrMs were initially identified from 6231 patients with stage IV NSCLC. Three hundred twenty-two cases with EGFR-positive non-squamous NSCLC and multiple BrMs were included. Among them, 208 cases who received either EGFR-TKIs plus bevacizumab or EGFR-TKIs alone as first-line treatment were enrolled into the final analysis (Fig. 1). Among the 208 patients, the median age was 59 years (range, 32–85 years), 56 (27%) were male, 32 (15%) were smokers, 11 (5%) had non-adenocarcinoma, 96 (46%) had EGFR 19DEL mutation, 98 (47%) had EGFR L858R mutation, 14 (7%) had EGFR rare mutations, 26 (13%) had ≥10 BrM and 75 (36%) were symptomatic. One hundred forty-nine received EGFR-TKIs, and 59 received EGFR-TKIs plus bevacizumab as first-line setting. Among them, 28 (47.5%) patients in the combined group received a dose of 15 mg/kg of bevacizumab. Baseline features of included patients are summarised in

Table 1
Baseline characteristics of the study population.

Variables	All cases	EGFR-TKI + bevacizumab		EGFR-TKI		*P* value
Total	208	59	28.37%	149	71.63%	
Age at diagnosis						
<65 years	147	42	28.57%	105	71.43%	0.919
≥65 years	61	17	27.87%	44	72.13%	
Gender						
Male	56	13	23.21%	43	76.79%	0.317
Female	152	46	30.26%	106	69.74%	
Smoking history						
Former/current smoker	32	7	21.88%	25	78.13%	0.376
Never-smoker	176	52	29.55%	124	70.45%	
ECOG performance status						
0–1	190	53	27.89%	137	72.11%	0.625
2	18	6	33.33%	12	66.67%	
N stage						
0	16	4	25.00%	12	75.00%	0.982
1	29	5	17.24%	24	82.76%	
2	80	23	28.75%	57	71.25%	
3	83	27	32.53%	56	67.47%	
Pathological classification						
Adenocarcinoma	197	56	28.43%	141	71.57%	0.794
Non-adenocarcinoma	11	3	27.27%	8	72.73%	
EGFR mutation						
19DEL	96	26	27.08%	70	72.92%	0.772
L858R	98	30	30.61%	68	69.39%	
Rare mutation	14	3	21.43%	11	78.57%	
Number of brain metastases						
<10	182	49	26.92%	133	73.08%	0.222
≥10	26	10	38.46%	16	61.54%	
EGFR-TKI choice						
Erlotinib	138	46	33.33%	92	66.67%	0.026
Gefitinib	56	13	23.21%	43	76.79%	
Icotinib	14	0	0.00%	14	100.00%	
Extracranial metastases						
Yes	185	54	29.19%	131	70.81%	0.616
No	23	5	21.74%	18	78.26%	
Symptoms						
Asymptomatic	133	38	28.57%	95	71.43%	0.930
Symptomatic	75	21	28.00%	54	72.00%	
Intracranial response rate						
ORR	101	39	38.61%	62	61.39%	0.001
DCR	178	53	29.78%	125	70.22%	0.272
Systematic response rate						
ORR	129	44	34.11%	85	65.89%	0.019
DCR	178	53	29.78%	125	70.22%	0.272

19DEL, Exon 19 deletion; L858R, Exon 21 Leu858Arg mutation; DCR, disease control rate; EGFR, epidermal growth factor receptor; ORR, objective response rate; TKI, tyrosine kinase inhibitor.

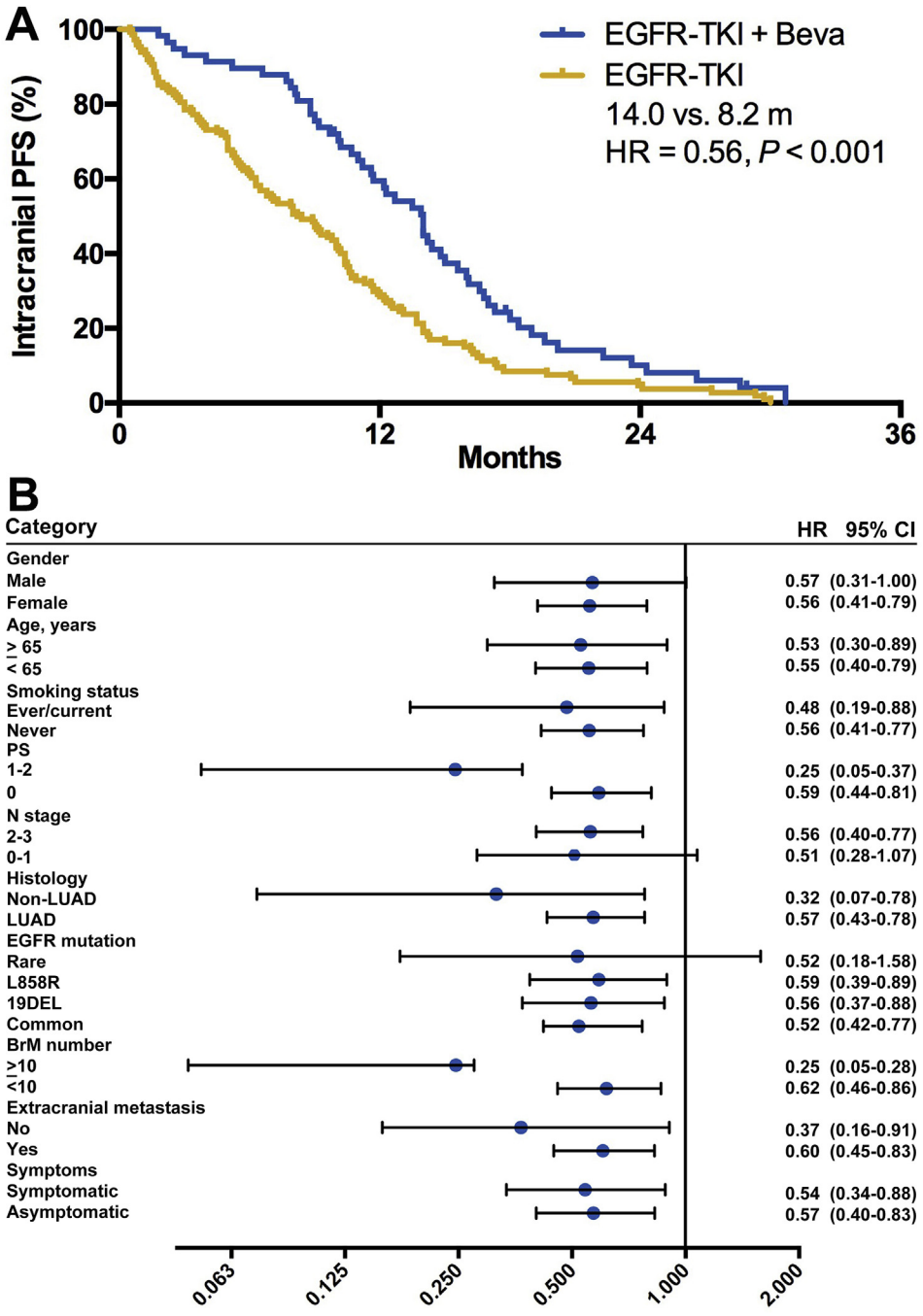

Fig. 2. **Intracranial PFS of EGFR-TKIs plus bevacizumab versus EGFR-TKIs alone in patients with EGFR-mutant NSCLC and multiple brain metastases. A,** Intracranial PFS was significantly longer in the combined therapy group than monotherapy group; **B,** subgroup analyses showed that this benefit were observed in the combined therapy group. 19DEL, exon 19 deletion; Beva, bevacizumab; BrM, brain metastasis; EGFR, epidermal growth factor receptor; HR, hazard ratio; L858R, exon 21 Leu858Arg mutation; NSCLC, non-small-cell lung cancer; OS, overall survival; PFS, progression-free survival; PS, performance status; TKI, tyrosine kinase inhibitor.

Table 1. There was no difference on clinicopathological characteristics between two treatment groups.

As to the efficacy, EGFR-TKIs plus bevacizumab was significantly associated with higher intracranial objective response rate (ORR, 66.1% vs. 41.6%, $P = 0.001$, Table 1), systemic ORR (74.6% vs. 57.1%, $P = 0.019$, Table 1), longer iPFS (14.0 vs. 8.2 months; HR = 0.56, $P < 0.001$; Fig. 2A) and sPFS (14.4 vs. 9.0 months; HR = 0.55, $P < 0.001$; Fig. 3A). More importantly, addition of bevacizumab was markedly associated with a longer OS (29.6 vs. 21.7 months; HR = 0.51, $P < 0.001$; Fig. 4A). All the subgroup analyses suggested iPFS (Fig. 2B), sPFS (Fig. 3B) and OS (Fig. 4B) benefit were observed in the combined

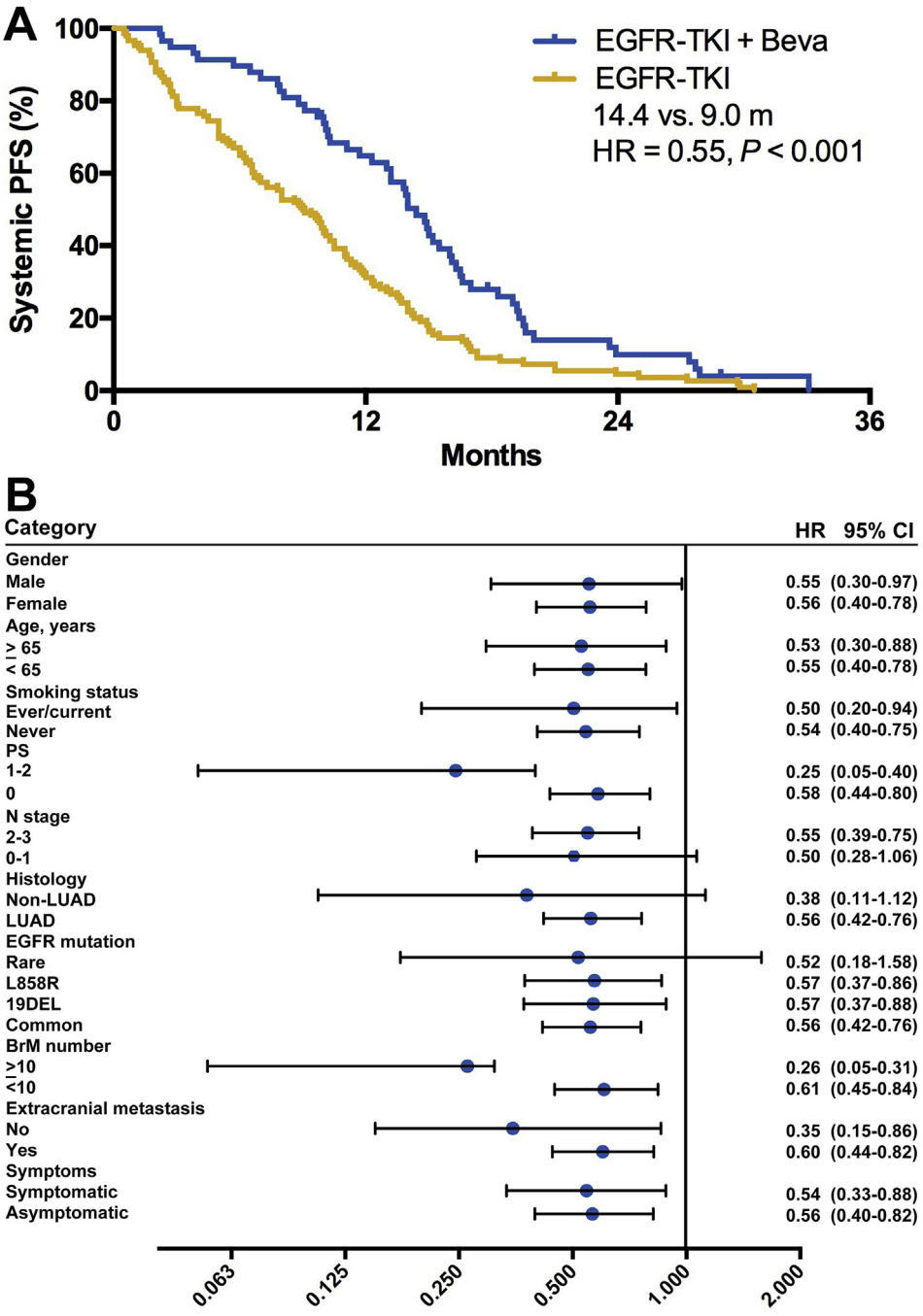

Fig. 3. **Systemic PFS of EGFR-TKIs plus bevacizumab versus EGFR-TKIs alone in patients with EGFR-mutant NSCLC and multiple brain metastases. A,** Systemic PFS was significantly longer in the combined therapy group than monotherapy group; **B,** subgroup analyses showed that systemic PFS benefit were observed in the combined therapy group. 19DEL, exon 19 deletion; Beva, bevacizumab; BrM, brain metastasis; EGFR, epidermal growth factor receptor; HR, hazard ratio; L858R, exon 21 Leu858Arg mutation; NSCLC, non-small-cell lung cancer; OS, overall survival; PFS, progression-free survival; PS, performance status; TKI, tyrosine kinase inhibitor.

treatment group. Patients with different types of EGFR mutations had similar iPFS, sPFS and OS benefit from combined therapy. Notably, patients with ≥10 BrMs had marginally significant iPFS and sPFS benefit from combined therapy more than those with <10 BrMs ($P_{interaction}$ = 0.052, $P_{interaction}$ = 0.083; respectively), but this should be treated with caution because of the limited sample size. The iPFS, sPFS and OS benefit from EGFR-TKIs plus bevacizumab were observed in patients with symptomatic and asymptomatic BrMs. Univariate analyses (Table 2) showed that intracranial ORR and addition of bevacizumab were significantly associated with longer iPFS. Systemic ORR and addition of bevacizumab were associated with significantly

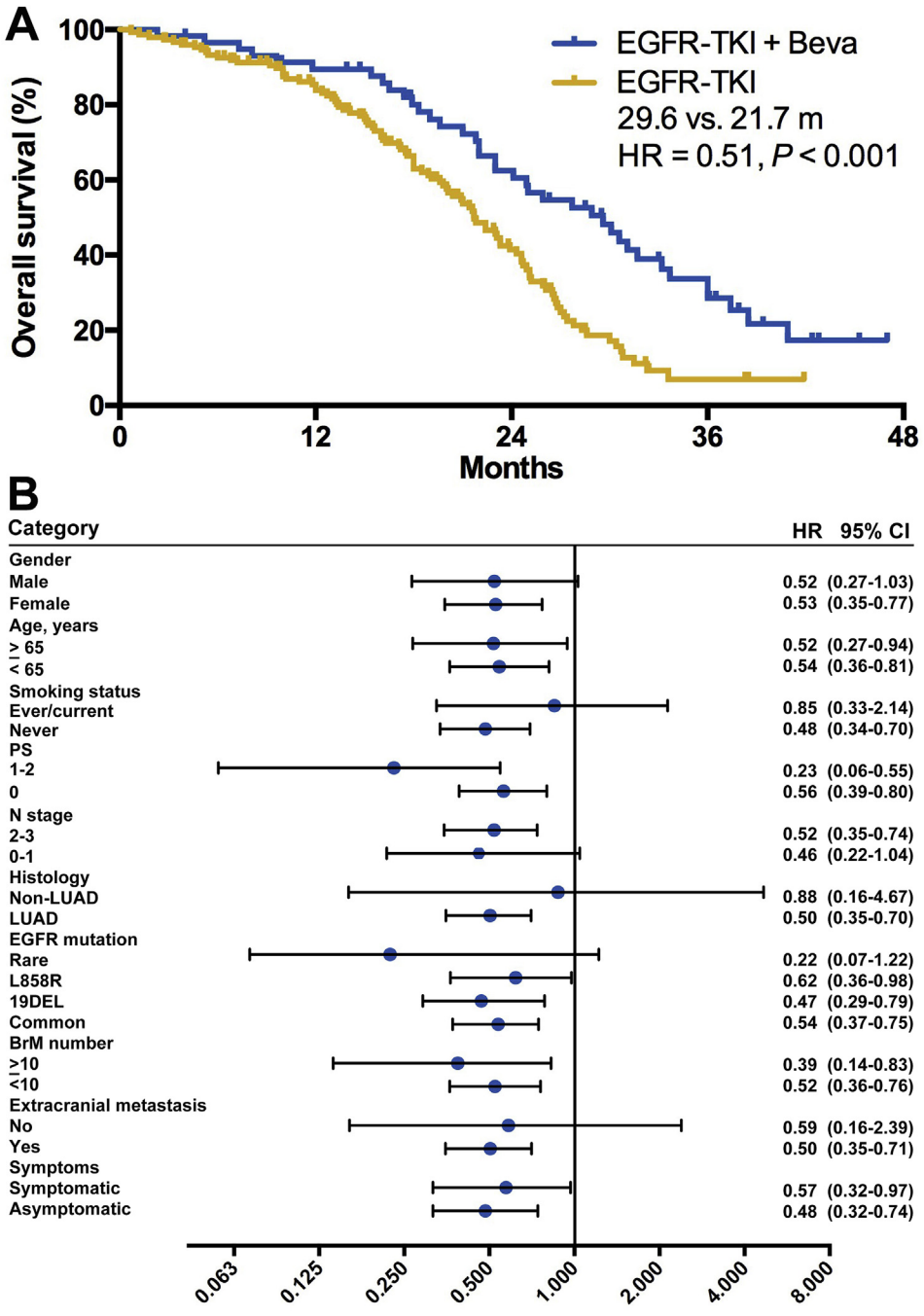

Fig. 4. **OS of EGFR-TKIs plus bevacizumab versus EGFR-TKIs alone in patients with EGFR-mutant NSCLC and multiple brain metastases. A,** OS was markedly prolonged in the EGFR-TKIs plus bevacizumab group than the TKIs monotherapy group; **B,** subgroup analyses showed that OS benefit was observed in the combined therapy group. 19DEL, exon 19 deletion; Beva, bevacizumab; BrM, brain metastasis; EGFR, epidermal growth factor receptor; HR, hazard ratio; L858R, exon 21 Leu858Arg mutation; NSCLC, non-small-cell lung cancer; OS, overall survival; PFS, progression-free survival; PS, performance status; TKI, tyrosine kinase inhibitor.

longer sPFS. Intracranial and systemic ORR and addition of bevacizumab were significantly associated with prolonged OS. Young age (<65 years) and ECOG PS = 0 subgroups had a marginally significantly longer OS ($P = 0.051$ and $P = 0.062$, respectively). Multivariate analyses (Table 2) revealed that addition of bevacizumab was independently associated with prolonged iPFS (HR = 0.546, $P < 0.001$), sPFS (HR = 0.457, $P < 0.001$) and OS (HR = 0.467, $P < 0.001$). In addition, intracranial ORR was associated with longer iPFS (HR = 0.564, $P < 0.001$) and systemic ORR was associated with markedly longer sPFS (HR = 0.411, $P < 0.001$) and OS (HR = 0.489, $P = 0.007$) in multivariate analyses.

Table 2
Univariate and multivariate analyses of clinical parameters on clinical outcomes.

Factor	Univariate analysis			Multivariate analysis		
	HR (log-rank)	95% CI	*P* value	HR (log-rank)	95% CI	*P* value
Intracranial progression-free survival						
Sex (female/male)	0.885	0.636–1.233	0.471			
Age (≥65 years/<65 years)	1.067	0.775–1.467	0.691			
Smoking (yes/no)	1.198	0.787–1.824	0.400			
ECOG PS (≥1/0)	1.200	0.727–1.980	0.477			
N stage (0/1–3)	0.814	0.471–1.406	0.461			
Histology (adeno/non-adeno)	0.741	0.402–1.368	0.338			
No. of BrM (<10/≥10)	0.858	0.558–1.318	0.484			
Extracranial metastasis (yes/no)	1.152	0.723–1.837	0.552			
EGFR mutation (common/rare)	0.923	0.533–1.598	0.775			
Intracranial RR (CR + PR/SD + PD)	0.561	0.421–0.749	<0.001	0.564	0.423–0.754	<0.001
Treatment (TKI + beva/TKI)	0.545	0.394–0.754	<0.001	0.546	0.394–0.756	<0.001
Systemic progression-free survival						
Sex (female/male)	0.858	0.616–1.196	0.367			
Age (≥65 years/<65 years)	1.048	0.762–1.441	0.775			
Smoking (yes/no)	1.193	0.783–1.818	0.413			
ECOG PS (≥1/0)	1.105	0.669–1.823	0.697			
N stage (0/1–3)	0.822	0.475–1.422	0.482			
Histology (adeno/non-adeno)	0.720	0.390–1.330	0.294			
No. of BrM (<10/≥10)	0.876	0.570–1.348	0.548			
Extracranial metastasis (yes/no)	1.103	0.692–1.759	0.680			
EGFR mutation (common/rare)	0.951	0.550–1.645	0.857			
Systemic RR (CR + PR/SD + PD)	0.465	0.347–0.625	<0.001	0.411	0.303–0.555	<0.001
Treatment (TKI + beva/TKI)	0.535	0.387–0.741	<0.001	0.457	0.326–0.642	<0.001
Overall survival						
Sex (female/male)	0.757	0.517–1.108	0.152			
Age (≥65 years/<65 years)	1.445	0.999–2.090	0.051	0.590	0.405–0.858	0.006
Smoking (yes/no)	1.216	0.745–1.987	0.434			
ECOG PS (≥1/0)	1.163	0.642–2.105	0.062	1.451	0.788–2.674	0.232
N stage (0/1–3)	0.962	0.505–1.835	0.908			
Histology (adeno/non-adeno)	0.927	0.431–1.993	0.846			
No. of BrM (<10/≥10)	0.678	0.421–1.093	0.110			
Extracranial metastasis (yes/no)	1.610	0.845–3.067	0.148			
EGFR mutation (common/rare)	0.705	0.343–1.448	0.341			
Systemic RR (CR + PR/SD + PD)	0.513	0.365–0.722	<0.001	0.489	0.290–0.824	0.007
Intracranial RR (CR + PR/SD + PD)	0.572	0.407–0.805	0.001	0.891	0.531–1.497	0.664
Treatment (TKI + beva/TKI)	0.482	0.325–0.713	<0.001	0.467	0.310–0.704	<0.001

HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; BrM, brain metastasis; EGFR, epidermal growth factor receptor; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; TKI, tyrosine kinase inhibitor; RR, response rate.

We further surveyed the efficacy of different types of EGFR-TKIs monotherapy or in combination with bevacizumab for these patients. As shown in Supplemental Fig. S1, iPFS (9.8 vs. 6.8 vs. 6.9 months, $P = 0.805$; Supplemental Fig. S1A), sPFS (10.0 vs. 8.0 vs. 6.4 months, $P = 0.626$; Supplemental Fig. S1B) and OS (23.3 vs. 18.5 vs. 20.1 months, $P = 0.332$; Supplemental Fig. S1C) were similar for different types of EGFR-TKIs monotherapy. Analogously, different types of EGFR-TKIs showed comparable iPFS (HR = 0.99, $P = 0.980$; Supplemental Fig. S1D), sPFS (HR = 1.16, $P = 0.685$; Supplemental Fig. S1E) and OS (HR = 1.02, $P = 0.970$; Supplemental Fig. S1F) when combined with bevacizumab.

No unexpected adverse effects were observed in this study (Supplemental Table S1). Fifty (84.7%) patients in the EGFR-TKIs plus bevacizumab group and 85 (57.0%) patients in the EGFR-TKIs monotherapy group had grade ≥III adverse effects. The most common adverse effects of any grade in the combined group were rash, hypertension, diarrhoea and paronychia, and those in the EGFR-TKIs monotherapy group were rash, diarrhoea, paronychia and liver function disorder or abnormal hepatic function. The frequent grade ≥III adverse effects in the combined group were hypertension, proteinuria, rash and liver function disorder or abnormal hepatic function, and those in the EGFR-TKIs monotherapy group were rash, paronychia, liver function disorder or abnormal hepatic function and hypertension. Among them, 19 (32.3%) of 59 patients discontinued bevacizumab because of adverse events. Twenty-six (44.1%) of 59 patients in the EGFR-TKIs plus bevacizumab group and 62 (41.6%) of 149 patients required dose reductions of EGFR-TKIs. Notably, there was no case with intracranial haemorrhage and severe haemoptysis in each group.

4. Discussion

Preclinical studies have shown that there existed cross-talk between EGFR and VEGF/VEGFR pathways, and simultaneous blockade of these two pathways could result in the inhibition of angiogenesis and progression in various solid tumours, such as NSCLC [8,9]. The synergistic effect of dual blockade of EGFR and VEGF/VEGFR pathways found in preclinical mouse model with EGFR mutations [11] have further been demonstrated in several clinical studies including BELIEF, JO25567 and NEJ026 study [12–14,21,22]. The phase II randomised JO25567 study first compared the efficacy of erlotinib plus bevacizumab versus erlotinib alone in patients with EGFR-mutant NSCLC and found that the median PFS was significantly prolonged in the combination group as first-line setting (16.0 vs. 9.7 months, HR = 0.54, $P = 0.0015$) [12]. This result was further reinforced by the phase III NEJ026 study in which combined group significantly prolonged PFS than erlotinib alone (median PFS 16.9 vs. 13.3 months, HR = 0.61, $P = 0.016$) [13]. The phase III clinical trial, named BEVERLY, to investigate first-line erlotinib plus bevacizumab versus erlotinib in patients with advanced NSCLC harbouring activating EGFR mutations is ongoing, and the result is also anticipated [23]. More recently, a multicentre randomised phase 3 study, named RELAY, reported that erlotinib plus ramucirumab (IgG1 monoclonal antibody against VEGFR2) significantly improved PFS than erlotinib plus placebo (median PFS 19.4 vs. 12.4 months, HR = 0.59, $P < 0.0001$) in EGFR-mutated metastatic NSCLC [24]. However, subsequent report did not observe OS benefit of the combination regimen in JO25567 study (HR = 0.81, $P = 0.326$) [14], and the mature OS data of NEJ026 and RELAY studies are eagerly awaited. Previously, several retrospective single-arm studies have reported the promising survival benefit of EGFR-TKIs plus bevacizumab in patients with EGFR-mutant NSCLC and BrM [15,16]. Therefore, it is necessary to further investigate the efficacy of this combination in comparison with EGFR-TKI monotherapy in those patients with multiple BrMs.

To the best of our knowledge, the present study was the largest one to directly compare the efficacy of EGFR-TKIs plus bevacizumab with EGFR-TKIs alone for patients with EGFR-mutant NSCLC and multiple BrMs. The results showed that EGFR-TKIs plus bevacizumab resulted in the significantly better intracranial and systemic ORR and PFS than EGFR-TKIs alone, which were in line with the previous study [11]. Moreover, we first found that addition of bevacizumab was associated with a significant prolongation of OS in this population. Subgroup analyses, including EGFR mutational type, the number of BrMs, symptoms and so on, indicated that iPFS, sPFS and OS benefit were consistently observed in the EGFR-TKIs plus bevacizumab group. Different types of EGFR-TKIs showed similar iPFS, sPFS and OS when combined with bevacizumab. A number of adverse effects associated with bevacizumab, including hypertension, proteinuria and hemorrhagic event, were more common in the EGFR-TKIs plus bevacizumab group than in the EGFR-TKIs alone group, but these were deemed to be acceptable and manageable. The proportion of patients with toxicities in each group were consistent with the level of toxicity observed in the JO25567 and NEJ026 study [12,13]. No unexpected serious adverse effects were observed in each group. Collectively, these findings suggest that the combination of EGFR-TKIs and bevacizumab could be an alternative therapeutic option for patients with EGFR-mutant NSCLC and multiple BrMs.

Previously, two studies reported that bevacizumab could delay the onset of BrM in both preclinical mouse model and patients with NSCLC [25,26], suggesting a potential therapeutic value of bevacizumab in patients with BrM. A prospective single-arm phase II study explored the efficacy and safety of bevacizumab plus first-line chemotherapy in patients with non-squamous NSCLC and asymptomatic untreated BrM and found an ORR of 62.7%, median PFS of 6.7 months and median OS of 16.0 months [27]. A recent retrospective study identified eight patients with EGFR-mutant NSCLC and BrM and reported an ORR of 100% (PR, n = 7; CR, n = 1) with a 2-year survival rate of 62.5% [16]. Interestingly, Feng *et al.* [15] found that bevacizumab significantly reduce circulating S100A9-positive monocytic myeloid-derived suppressor cells (MDSCs). Circulating MDSCs could be recruited to the normal brain microenvironment and thus play a critical role in brain metastatic niche formation [28], which partially explained the significant PFS and OS prolongation of bevacizumab plus EGFR-TKIs therapy in patients with EGFR-mutant lung adenocarcinoma and BrM [15]. In addition, patients with multiple BrMs usually suffered from encephaledema or intracranial hypertension, which could lead to a dismal prognosis. Bevacizumab could rapidly and effectively control these symptoms and then improve the overall prognosis [29–31]. Notably, both PFS and OS in our study was shorter than those reported in JO25567 and NEJ026 studies, which may be caused by a higher proportion of patients with symptomatic BrM (36%) and EGFR rare mutations (7%) in our study.

Currently, third-generation EGFR-TKIs (e.g. osimertinib) with improved CNS penetration and activity showed the superior CNS efficacy than first-generation EGFR-TKIs in patients with EGFR-mutant BrM [6,7]. It has become the new standard of care for first-line setting of advanced or metastatic EGFR-mutant NSCLC. Basically, osimertinib should also be the

preferred choice for patients with EGFR-mutant NSCLC and BrM. However, the limited therapeutic options beyond osimertinib remind us that more efficacious alternatives are urgently needed. Similar to JO25567 and NEJ026 studies, preliminary results from phase I/II showed that osimertinib plus bevacizumab or combined with ramucirumab (anti-VEGFR2 monoclonal antibody) is promising [32]. Therefore, it is worthwhile exploring the efficacy of bevacizumab plus new-generation EGFR-TKIs (e.g. osimertinib) in patients with EGFR-mutant NSCLC and multiple BrM in the future.

Although these results had significant therapeutic implications, several limitations should be mentioned in this study. First, the sample size was small and the retrospective feature of this study will inevitably have selection bias. Thus, the results should be interpreted with caution and large-scale study, especially a prospective one, is still needed. Second, patients who received previous cranial radiotherapy and those with less than 3 brain metastatic lesions were not included; therefore, the findings in the present study might not be generalisable to the whole population with BrM. Third, EGFR T790M status, total volume of BrM, other comorbidities and subsequent regimen (e.g. cranial radiotherapy or osimertinib) after failure to EGFR-TKI plus bevacizumab or EGFR-TKIs treatment were not well recorded in detail, leading to the bias of OS estimation. Last but not least, all the eligible patients received the first-generation EGFR-TKIs, while the impact of new-generation EGFR-TKI plus bevacizumab or alone on OS in patients with multiple BrM needs further investigation.

In conclusion, this study found that bevacizumab plus EGFR-TKIs could significantly prolong not only PFS but also OS in patients with EGFR-mutant NSCLC and multiple BrMs when compared with EGFR-TKIs alone, indicating that patients with EGFR-mutant NSCLC and multiple BrMs might have a subpopulation benefit more from the combination of EGFR-TKIs and bevacizumab. Further large-scale prospective study is needed to validate our finding in patients with EGFR-mutant NSCLC and multiple BrMs.

Author contributions

Cai.Z. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. T.J. and Cai.Z. contributed to the study concept and design and drafting of the manuscript. T.J., Y.Z., X.C. and C.S. performed statistical analysis. S.R. and Cai.Z. obtained funding. T.J., S.R. and Cai.Z. performed study supervision. All authors contributed to Acquisition, analysis or interpretation of data; critical revision of the manuscript for important intellectual content and administrative, technical or material support.

Additional contributions

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Conflict of interest statement

None declared.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2019.08.021.

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