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ORIGINAL ARTICLE

Real world study of the continuation of bevacizumab beyond disease progression after first-line treatment containing bevacizumab in Chinese patients with advanced non-small cell lung cancer

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Keywords
Bevacizumab; beyond progression; non-small cell lung cancer; overall survival; safety.

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Abstract

Background: Bevacizumab (Bev) plus platinum-based chemotherapy is a standard first-line treatment option for advanced non-squamous non-small cell lung cancer (NS-NSCLC). We evaluated the efficacy and safety of continuing Bev in Chinese patients with advanced NS-NSCLC progression after first-line treatment containing Bev in a real-world setting.

Methods: The data of 118 patients with advanced NS-NSCLC who received Bev between July 2009 and July 2017 were retrospectively collected. The patients were divided into groups: 15 in Bev first-line, 82 in Bev ≥ second-line, and 21 in Bev cross-lines. The primary endpoint was overall survival; secondary objectives were progression-free survival, objective response rate, disease control rate, and safety.

Results: The overall survival was 21.8, 32.5, and 18.9 months (P = 0.092) in the overall population and 39.3, 25.8, and 15.0 months (P = 0.347) in the wild-type population in the Bev first-line, Bev ≥ second-line, and Bev cross-lines groups, respectively. There were no significant differences in progression-free survival of second-line treatment between the groups in the overall population: 2.6, 3.7, and 3.2 months in the Bev first-line, Bev ≥ second-line, and Bev cross-lines groups, respectively (P = 0.796). No statistically significant improvement in objective response or disease control rates in the Bev cross-lines group was observed. No unexpected or severe adverse events were recorded.

Conclusion: We found no benefit in continuing Bev treatment beyond progression after first-line treatment containing Bev for patients with advanced NS-NSCLC. Further research of validated predictive biomarkers of response to treatment after long-term antiangiogenic therapy is required.

Introduction

Non-small cell lung cancer (NSCLC) accounts for over 85% of lung cancer diagnoses,[1] and is the most common cancer and leading cause of cancer-related death worldwide.[2] The majority of NSCLC patients present with advanced stage at diagnosis and thus have a poor prognosis.[3] For several years, platinum-based doublet chemotherapy regimens have been the standard first-line treatment for advanced NSCLC.[4] More recently, the superior results of large-scale randomized trials[5–8] and real world studies[9,10] have placed bevacizumab (Bev), a monoclonal antibody that inhibits the vascular endothelial growth factor (VEGF),[11] in combination with platinum-based chemotherapy as the standard first-line therapy for non-squamous (NS)-NSCLC, particularly for patients who do not harbor targetable alterations, such as *EGFR* mutations, or *ALK* or *ROS1* rearrangements. Currently, there is no standard treatment regimen for patients who experience disease progression after first-line treatment.

Evidence from preclinical and clinical studies has shown that the continuation of Bev combined with chemotherapy might be a second-line treatment option. Preclinical data suggests that VEGF is continuously expressed during tumor growth and tumor progression, and persistent VEGF inhibition achieves and maintains tumor regression and delays tumor growth.[12–17] This concept has been supported by the data of patients with metastatic colorectal cancer in the clinical setting. Two non-randomized observational cohort studies (BRiTE[18] and ARIES[19]) reported that the continuation of Bev beyond first progressive disease (PD) of first-line Bev plus chemotherapy could improve post-progression survival. AvaALL (MO22097), the first randomized phase IIIb study assessing the efficacy of continued Bev beyond PD after first-line treatment in NSCLC showed prolonged progression-free survival (PFS) in third-line treatment, but no statistically significant improvement in overall survival (OS) in patients continuing Bev across multiple treatment lines compared to patients who received chemotherapy alone in subsequent lines.[20] Although an increasing number of studies have explored the continuation of Bev, limited data are available on Bev continuation in subsequent lines of treatment after first PD in patients with NSCLC in a real world setting. Whether long-term Bev can prolong OS in NSCLC patients is unknown. This prompted us to perform a retrospective study to evaluate the continuation of Bev in treatment lines beyond first PD versus first and later line treatment containing Bev in patients with advanced NS-NSCLC.

Methods

Data source and study population

The records of patients with advanced NS-NSCLC who received Bev between July 2009 and July 2017 were retrospectively collected from the Cancer Hospital, Chinese Academy of Medical Sciences (Beijing, China). Eligible patients were required to be histologically or cytologically confirmed with stage IIIB or IV (American Joint Committee on Cancer 7th Edition Cancer Staging Manual) NS-NSCLC. Study subjects were classified into three mutually exclusive groups according to treatment: (i) Bev first-line (Bev1): patients who received treatment containing Bev as first-line therapy but no further Bev in second-line treatment after first PD; (ii) Bev ≥ second-line (Bev2), patients who received first-line therapy without Bev, but received Bev in later-lines of treatment; and (iii) Bev cross-lines (BevCL), patients who received treatment containing Bev as first-line therapy and continued Bev for a second line of treatment beyond first PD. A total of 118 patients were included in the study. Baseline characteristics were collected for each patient, including age, gender, Eastern Cooperative Oncology Group performance status (ECOG PS), smoking history, histology, disease stage, *EGFR* status, *ALK* status, brain metastasis, and concomitant regimens.

Assessment

This was a retrospective study with a primary outcome of OS and secondary objectives of PFS, objective response rate (ORR), disease control rate (DCR), and safety assessment in NS-NSCLC patients who were administered Bev treatment beyond PD after first-line treatment containing Bev. OS was defined as the interval from the initiation of first-line treatment until death, regardless of cause. PFS1 and PFS2 were defined as the interval from the start of first-line treatment to first PD and from the start of second-line treatment to second PD or death from any cause, whichever occurred first, respectively. Disease response to treatment was assessed according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. ORR was defined as the percentage of patients achieving a complete response (CR) or partial response (PR), while DCR was defined as the percentage of patients achieving a CR, PR, or stable disease (SD) for ≥ 6 weeks. ORR1 and DCR1 refer to disease response to first-line treatment, while ORR2 and DCR2 refer to disease response to second-line treatment. In subgroup analysis, the wild-type subgroup refers to *EGFR* negative/*ALK* negative, *EGFR* negative/*ALK* unknown, and *EGFR* unknown/*ALK* negative populations. Adverse events (AEs) were recorded according to Common Terminology Criteria for Adverse Events version 4.0. The frequency of Bev-related AEs (gastrointestinal perforation, wound healing complications, bleeding, hypertension, proteinuria, and thromboembolic events) was also assessed.

Statistics analysis

The distribution of patients' baseline demographic/clinical characteristics (age, gender, ECOG PS, smoking status, histology, disease stage, *EGFR*/*ALK* status, brain metastasis) and treatment patterns were described using frequency analysis. Fisher's exact and chi-square tests were used for categorical variables and a Student's *t*-test for continuous variables to compare the differences among the treatment groups at baseline. PFS and OS were analyzed using the Kaplan–Meier method, while the survival curves were compared using a log-rank test (Figs 1–4). ORR and DCR were compared using Fisher's exact and chi-square tests. All statistical analysis was performed

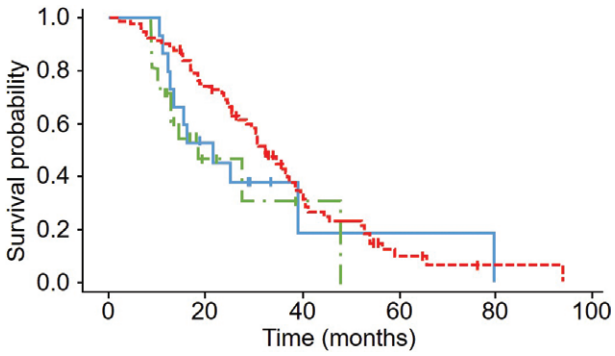

Figure 1 Kaplan-Meier curves for OS in Bev 1st line group, Bev ≥2nd line group and Bev cross-lines group of overall population. Bev, bevacizumab; OS, overall survival. (——) Bev 1st line group, (------) Bev ≥2nd line group, and (- - - -) Bev cross-lines group.

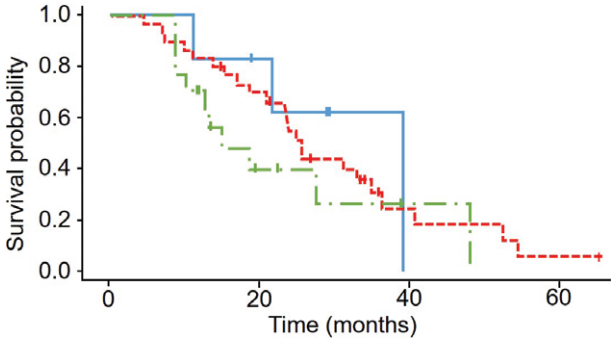

Figure 2 Kaplan-Meier curves for OS in Bev 1st line group, Bev ≥2nd line group and Bev cross-lines group of wild-type population. Bev, bevacizumab; OS, overall survival. (——) Bev 1st line group, (------) Bev ≥2nd line group, and (- - - -) Bev cross-lines group.

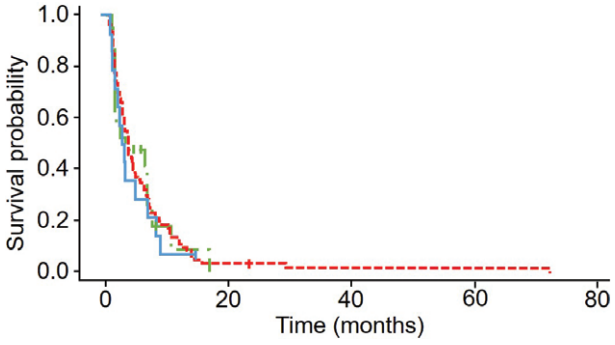

Figure 3 Kaplan-Meier curves for PFS2 in Bev 1st line group, Bev ≥2nd line group and Bev cross-lines group of overall population. PFS2, progression-free survival of second-line treatment; Bev, bevacizumab. (——) Bev 1st line group, (------) Bev ≥2nd line group, and (- - - -) Bev cross-lines group.

using SAS 9.4 (SAS Institute Inc., Cary, NC, USA) and alpha = 0.05 was used as a significance level in all statistical testing.

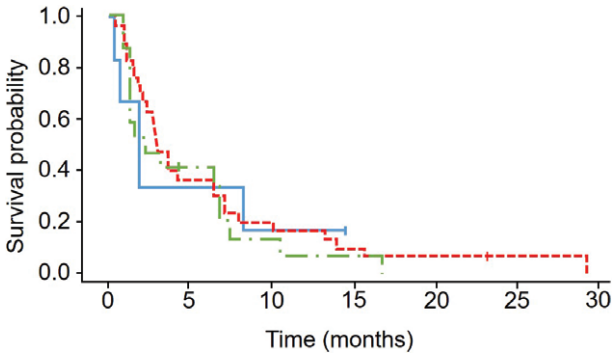

Figure 4 Kaplan-Meier curves for PFS2 in Bev 1st line group, Bev ≥2nd line group and Bev cross-lines group of wild-type population. PFS2, progression-free survival of second-line treatment; Bev, bevacizumab. (——) Bev 1st line group, (------) Bev ≥2nd line group, and (- - - -) Bev cross-lines group.

Results

Patients and characteristics

From July 2009 to July 2017, a total of 118 patients met the study criteria: 15 in Bev1, 82 in Bev2, and 21 in the BevCL group. The enrolled patients were relatively young (median age 52 years) and most were male, smokers, with ECOG PS 0 or 1, stage IV disease, and adenocarcinoma histology. Chemotherapy was the base concomitant treatment in both first and second lines of therapy in all three groups. The most common combined regimen was pemetrexed-based chemotherapy in first-line treatment. With regard to second-line combined chemotherapy, 6.7%, 24.4%, and 33.3% of patients in each group received docetaxel, respectively. Regimens other than chemotherapy, such as *EGFR*/*ALK* tyrosine kinase inhibitors (TKIs) and immunotherapy combined with or without Bev, were also administered. The baseline demographics and clinical characteristics of patients were well balanced between the groups, with the exception of an imbalance in *EGFR*/*ALK* status and concomitant regimens received during the study (Table 1).

Clinical outcomes

At data cutoff (18 April 2018), the median follow-up duration was 25.6 months. In the overall population, the median OS was 21.8, 32.5, and 18.9 months (P = 0.092) in the Bev1, Bev2, and Bev CL groups, respectively. Continued Bev treatment in the BevCL group was not superior over the other two patterns of Bev treatment. In the wild-type subgroup, OS was 25.8 and 15.0 months in the Bev2 and BevCL groups, respectively, compared to 39.3 months in the Bev1 group (P = 0.347). No OS improvement in patients receiving BevCL was observed in subgroup analysis (Table 2).

Table 1 Baseline characteristics of NS-NSCLC patients at first-line therapy

Characteristics	No. of patients (%)				*P*
	All (*n* = 118)	Bev first-line (*n* = 15)	Bev ≥ 2nd line (*n* = 82)	Bev cross-lines (*n* = 21)	
Age, years					0.718
Median	52	52	52	53	—
Mean	52.8	53.5	52.4	54.2	—
Range	25–75	34–73	25–75	37–69	—
Gender					0.851
Male	81 (68.6)	11 (73.3)	55 (67.1)	15 (71.4)	—
Female	37 (31.4)	4 (26.7)	27 (32.9)	6 (28.6)	—
ECOG PS					0.195
0	39 (33.1)	4 (26.7)	26 (31.7)	9 (42.9)	—
1	76 (64.4)	10 (66.7)	54 (65.9)	12 (57.1)	—
2	3 (2.5)	1 (6.7)	2 (2.4)	0	—
Smoking status†					0.970
Non-smoker	51 (43.2)	7 (46.7)	35(42.7)	9 (42.9)	—
Former/current smoker	62 (52.5)	8 (53.3)	42 (51.2)	12 (57.1)	—
Histology					0.545
Adenocarcinoma	108 (91.5)	15 (100)	74 (90.2)	19 (90.5)	—
Others	10 (8.5)	0	8 (9.8)	2 (9.5)	—
Disease stage					0.639
IIIB	17 (14.4)	0	15 (18.3)	2 (9.5)	—
IV	101 (85.6)	15 (100)	67 (81.7)	19 (90.5)	—
Driver mutation test					
EGFR					0.049
EGFR positive	29 (24.6)	5 (33.3)	21 (25.6)	3 (14.3)	—
EGFR non-positive‡	89 (75.4)	10 (66.7)	61 (74.4)	18 (85.7)	—
ALK					0.000
ALK positive	11 (9.3)	1 (6.7)	10(12.2)	0	—
ALK non-positive§	107 (90.7)	14 (93.3)	72 (87.8)	21 (100.0)	—
Brain metastasis					0.285
Yes	13 (11.0)	0	10 (12.2)	3 (14.3)	—
No	105 (89.0)	15 (100)	72 (87.8)	18 (85.7)	—
First-line regimen					
TKI	19 (16.1)	0	19 (23.2)	0	0.004
Mono-chemotherapy					
Pemetrexed-based	0	0	0	0	—
Paclitaxel-based	0	0	0	0	—
Doublet-chemotherapy					0.009
Pemetrexed-based	71 (60.2)	13 (86.7)	41 (50.0)	17 (81.0)	—
Paclitaxel-based	10 (8.5)	0	8 (9.8)	2 (9.5)	—
Second-line regimen					
TKI	24 (20.3)	8 (53.3)	14 (17.1)	2 (9.5)	0.005
Mono-chemotherapy					0.316
Docetaxel-based	15 (12.7)	1 (6.7)	9 (11.0)	5 (23.8)	—
Pemetrexed-based	7 (5.9)	0	5 (6.1)	2 (9.5)	—
Doublet-chemotherapy					0.031
Docetaxel-based	13 (11.0)	0	11 (13.4)	2 (9.5)	—
Pemetrexed-based	27 (22.9)	2 (13.3)	24 (29.3)	1 (4.8)	—

†Data was missing for five patients. ‡*EGFR* non-positive included *EGFR* negative and *EGFR* unknown patients. §*ALK* non-positive included *ALK* negative and *ALK* unknown patients. ECOG PS, Eastern Cooperative Oncology Group performance status; NS-NSCLC, non-squamous non-small cell lung cancer; TKI, tyrosine kinase inhibitor.

In first-line therapy, PFS1 was longer in both the Bev1 and BevCL groups compared to the Bev2 group (7.6, 6.3, and 5.7 months, respectively; $P = 0.500$). In the overall population, the ORR1 and DCR1 in the Bev1 and BevCL groups were higher than in the Bev2 group (ORR1 60.0%, 57.1%, and 37.8%; DCR1 100.0%, 85.7%, and 76.8%, respectively).

With regard to second-line treatment, there were no significant differences in PFS2 between the groups in the

Table 2 OS of different types of patients

Types of patients	Treatments	Median OS (months)	Log-rank *P*
Overall population	Bev first-line	21.8	0.092
	Bev ≥ second-line	32.5	
	Bev cross-lines	18.9	
Wild-type population	Bev first-line	39.3	0.347
	Bev ≥ second-line	25.8	
	Bev cross-lines	15.0	
ECOG PS 0	Bev first-line	13.7	0.000
	Bev ≥ second-line	38.9	
	Bev cross-lines	18.9	
ECOG PS 1–2	Bev first-line	39.3	0.631
	Bev ≥ second-line	30.4	
	Bev cross-lines	27.6	

ECOG PS, Eastern Cooperative Oncology Group performance status; OS, overall survival.

overall population: 2.6, 3.7, and 3.2 months in the Bev1, Bev2, and BevCL groups, respectively ($P = 0.796$). Analysis of PFS2 in the subgroups produced results that were consistent to those for the overall population, and no significant benefit of BevCL was observed in subgroup analysis of wild-type, ECOG PS 0, and ECOG PS 1–2 populations (Table 3). Patients who continued Bev therapy had better ORR2 (19.0%) than those who initiated non-Bev therapy in the Bev1 group (6.7%), and the ORR2 in the Bev2 group was 22.0% ($P = 0.388$). DCR2 was 57.1% in the BevCL group, compared to 66.7% and 64.6% in the Bev1 and Bev2 groups, respectively ($P = 0.788$). There was no statistically significant difference in ORR2 and DCR2 either in the overall population or in subgroup analysis (Table 4).

The continuation of Bev beyond progression did not significantly improve OS, PFS, ORR, or DCR in the overall population or in subgroup analysis.

Table 3 PFS of different types of patients in second-line treatment

Types of patients	Treatments	Median PFS2 (months)	Log-rank *P*
Overall population	Bev 1st line	2.6	0.796
	Bev ≥ 2nd line	3.7	
	Bev cross-lines	3.2	
Wild-type population	Bev 1st line	1.9	0.780
	Bev ≥ 2nd line	3.0	
	Bev cross-lines	2.3	
ECOG PS: 0	Bev 1st line	1.1	0.215
	Bev ≥ 2nd line	4.1	
	Bev cross-lines	2.3	
ECOG PS: 1–2	Bev 1st line	2.6	0.982
	Bev ≥ 2nd line	3.5	
	Bev cross-lines	6.5	

ECOG PS, Eastern Cooperative Oncology Group performance status; PFS, progression-free survival.

Safety

Safety analysis was conducted in the whole population. The most common AEs were myelosuppression and gastrointestinal disorders in all three groups. The majority of AEs were grade 1 or 2, and the most commonly reported grade 3/4 AEs were leukopenia and neutropenia. In terms of chemotherapy-related AEs, myelosuppression and gastrointestinal disorders were more frequently observed in patients treated with BevCL. As for Bev-specific toxicities, proteinuria (3 patients), epistaxis (2 patients) and hematochezia (1 patient) were reported in the BevCL group, compared to epistaxis (2 patients) and hypertension (1 patient) in the other two groups. One patient in the BevCL group discontinued Bev because of grade 1 interstitial pneumonia. No drug-related deaths or unexpected safety issues were observed. Table 5 shows the incidence of AEs in our study.

Discussion

This study aimed to verify the efficacy and safety of continuing Bev beyond disease progression after first-line treatment containing Bev in patients with advanced NS-NSCLC in the real world. In general, the clinical outcomes of continuous BevCL in our study were poor, with ORR2 of 19.0%, DCR2 of 57.1%, and median PFS2 of 3.2 months in second-line therapy, with a median OS of 18.9 months. The continuation of Bev in a second-line regimen did not provide ORR, DCR, PFS, or OS benefits in patients with advanced NS-NSCLC.

Preclinical data has demonstrated that VEGF is continuously expressed during tumor growth and tumor progression, and longer anti-angiogenesis leads to delayed tumor growth.[16,17] Thus Bev, an anti-VEGF monoclonal antibody, may continue to be effective after the development of resistance to chemotherapy. This hypothesis is supported by the results of pivotal clinical trials exploring the benefit of Bev continuation following initial progression for some cancer patients, including BRiTE,[18] ARIES,[19] BEBYP[21] and ML18147[22] trials in advanced colorectal cancer, and TANIA[23] in advanced breast cancer. The correlation between the continuation of Bev following initial progression after first-line therapy and antitumor activity was also evaluated in NSCLC. The West Japan Oncology Group (WJOG) 5910L conducted a multicenter, randomized, phase II trial in NSCLC patients whose disease had progressed after first-line treatment with Bev plus a platinum-based doublet. The study demonstrated improved PFS of treatment with docetaxel plus Bev in comparison to patients receiving docetaxel alone (median PFS 4.4 vs. 3.4 months; $P = 0.058$).[24] In the multicenter, randomized, phase III AvaALL trial, NSCLC patients whose disease

Table 4 ORR and DCR in the overall and wild type population, and patients with ECOG PS 0 and ECOG PS 1–2

		No. of patients (%)			
Type of patients	Index	Bev first-line (n = 15)	Bev ≥ second-line (n = 82)	Bev cross-lines (n = 21)	P
Overall population	ORR1	9/15 (60.0)	31/82 (37.8)	12/21 (57.1)	0.116
	DCR1	15/15 (100.0)	63/82 (76.8)	18/21 (85.7)	0.090
	ORR2	1/15 (6.7)	18/82 (22.0)	4/21 (19.0)	0.388
	DCR2	10/15 (66.7)	53/82 (64.6)	12/21 (57.1)	0.788
Wild-type population	ORR2	0/6 (0)	4/30 (13.3)	2/17 (11.8)	1.000
	DCR2	3/6 (50.0)	19/30 (63.3)	9/17 (52.9)	0.661
ECOG PS 0	ORR2	0/4 (0)	6/26 (23.1)	1/9 (11.1)	0.552
	DCR2	3/4 (75.0)	18/26 (69.2)	5/9 (55.6)	0.871
ECOG PS 1–2	ORR2	1/11 (9.1)	12/56 (21.4)	3/12 (25.0)	0.684
	DCR2	7/11 (63.6)	35/56 (62.5)	7/12 (58.3)	1.000

DCR, disease control rate; ECOG PS, Eastern Cooperative Oncology Group performance status; ORR, overall response rate.

Table 5 Adverse events

Type of AE	AE grade	Total report	Bevfirst-lineNo. (%)	Bev≥ second-lineNo. (%)	Bevcross-linesNo. (%)
Total	≥ 3	29	5	18	6
Anemia	1	8	0 (0.0)	5 (6.1)	3 (14.3)
	2	10	0 (0.0)	5 (6.1)	5 (23.8)
	3	4	1 (6.7)	2 (2.4)	1 (4.8)
Leukopenia	1	8	1 (6.7)	2 (2.4)	5 (23.8)
	2	12	0 (0.0)	7 (8.5)	5 (23.8)
	3	10	2 (13.3)	7 (8.5)	1 (4.8)
Neutropenia	1	11	1 (6.7)	7 (8.5)	3 (14.3)
	2	15	2 (13.3)	6 (7.3)	7 (33.3)
	3	11	1 (6.7)	6 (7.3)	4 (19.0)
	4	1	1 (6.7)	0 (0.0)	0 (0.0)
Thrombocytopenia	1	7	2 (13.3)	3 (3.7)	2 (9.5)
	2	5	1 (6.7)	1 (1.2)	3 (14.3)
	4	2	0 (0.0)	2 (2.4)	0 (0.0)
Leukomonocyte count decreased	1	1	0 (0.0)	1 (1.2)	0 (0.0)
	2	1	0 (0.0)	1 (1.2)	0 (0.0)
Nausea	1	39	5 (33.3)	25 (30.5)	9 (42.9)
	2	16	0 (0.0)	9 (11.0)	7 (33.3)
Vomiting	1	19	2 (13.3)	10 (12.2)	7 (33.3)
	2	12	0 (0.0)	8 (9.8)	4 (19.0)
Mucositis oral	1	1	0 (0.0)	1 (1.2)	0 (0.0)
	2	3	1 (6.7)	1 (1.2)	1 (4.8)
Loss of appetite	1	47	4 (26.7)	28 (34.1)	15 (71.4)
	2	8	0 (0.0)	7 (8.5)	1 (4.8)
	3	1	0 (0.0)	1 (1.2)	0 (0.0)
Diarrhea	1	1	0 (0.0)	1 (1.2)	0 (0.0)
	2	1	0 (0.0)	1 (1.2)	0 (0.0)
Rash	1	3	0 (0.0)	2 (2.4)	1 (4.8)
	2	2	1 (6.7)	1 (1.2)	0 (0.0)
Constipation	1	4	1 (6.7)	3 (3.7)	0 (0.0)
ALT increased	1	8	1 (6.7)	1 (1.2)	6 (28.6)
	2	1	0 (0.0)	1 (1.2)	0 (0.0)
AST increased	1	8	0 (0.0)	2 (2.4)	6 (28.6)

AEs, adverse events; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

progressed after first-line treatment with Bev plus a platinum-based doublet treatment were randomized in a 1:1 ratio to one of two study arms.[20] Patients treated in arm A received Bev plus the investigator's choice of agents indicated for use in second and subsequent lines of treatment. Patients treated in arm B received the investigator's choice of agents alone indicated for use in second and subsequent lines of treatment, but no further Bev treatment.

The results showed statistically prolonged PFS3 in the Bev plus standard of care (SOC) compared to the SOC alone group in third-line treatment (4.0 vs. 2.6 months; $P = 0.0045$).

These results indicate that the continuation of Bev could enhance the antitumor activity of standard therapy for NSCLC patients after the failure of first-line treatment with a regimen containing Bev. However, prior preclinical evidence suggests that long-term anti-angiogenic therapy blocks tumor blood supply, causes an imbalance between oxygen supply and consumption, and ultimately results in hypoxia in the microenvironment of the tumor.[25,26] Under hypoxia, hypoxia-inducible factor 1-alpha transcription is upregulated, activating VEGF transcription, inducing alternate proangiogenic growth factors and promoting the formation of abnormal blood vessels. This vicious cycle further exacerbates tumor hypoxia and in turn results in tumor growth.[27–32] Based on this hypothesis, whether prolonging PFS could translate into an OS benefit with Bev beyond disease progression in advanced NSCLC is still under debate. WJOG 5910L showed a longer OS of 13.1 months in the docetaxel plus Bev group versus 11.0 months in the docetaxel group, with a hazard ratio of 0.74 and a stratified log-rank P value of 0.11, which met the predefined criteria for statistical significance ($P < 0.2$).[24] In the AvaALL study, however, OS was not significantly increased with Bev continuation versus SOC alone (11.86 vs. 10.22 months; $P = 0.1044$).[20] Little real-world data exists exploring the efficacy of Bev beyond first PD in NSCLC in terms of OS.

Overall, our data tended to be different to the results obtained in randomized trials for cross-line Bev in combination with chemotherapy. In the overall population, the superiority of OS improvement in the Bev2 group may largely be attributed to the fact that 25.6% and 12.2% of patients were *EGFR* and *ALK* positive, respectively, and were thus treated with TKIs. OS was significantly longer in the Bev2 compared to the Bev1 group in *EGFR*/*ALK* (+) subgroup analysis (35.0 vs. 13.0 months; $P = 0.007$). Previous studies have demonstrated a survival benefit in patients with *EGFR* mutations treated with Bev plus EGFR-TKIs or EGFR-TKIs alone compared to chemotherapy.[33–35] In addition, the imbalance of characteristics of concomitant regimens may also have led to the relatively poor results of our BevCL group, as mono-chemotherapy was the main concomitant regimen in this group considering the tolerability of Bev compared to doublet-chemotherapy in the Bev2 group. However, our results in the wild-type population showed no survival benefit in patients who underwent continuous Bev beyond first PD, in either PFS2 (2.3 months) or OS (15.0 months). It is possible that unaccounted factors may have impacted the choice of subsequent therapy and concomitant regimens made by treating oncologists, which in turn may have biased the outcome in patients continuing Bev. Comorbidities, such as cardiovascular disease, uncontrolled hypertension, coagulopathy, and a history of thromboembolic or hemorrhagic events may also impact physicians' treatment decisions, thus potentially introducing biases in terms of patient selection. The BevCL group results in wild-type subgroup analysis were inferior to the results reported in the AvaALL trial (PFS2 of 5.5 and OS of 11.9 months [OS was defined as the interval from the date of randomization at first PD to the date of death]).[20] The different inclusion criteria and patients' general condition may explain these differences. Our data may better reflect current medical practice and choices of agents indicated for use in second and subsequent lines of treatment in a wild-type population. The ORR2 and DCR2 in the BevCL group in this study were 19.0 and 57.1%, respectively, which were lower than that reported in Japanese WJOG 5910L trial of second-line therapies (36% ORR, 62% of DCR). [24] None of the second-line therapies used in either the WJOG 5910L trial or our study showed significantly improved response rates compared to patients who were not treated with BevCL. No increased response rates were observed in our subgroup analysis of the BevCL group.

The results of our analysis should be interpreted with caution because of the small sample size and clinical choice selection bias. Further research is warranted as to whether continuous Bev is the optimal treatment in patients with NS-NSCLC with PD after first-line therapy, especially in a wild-type population.

The safety of long-term exposure to Bev was another issue explored in this study. The type and frequency of grade 3/4 AEs (including myelosuppression and loss of appetite) in the BevCL group were consistent with the other two groups and the known safety profile of chemotherapy regimens. Despite the long exposure to Bev, patients in the BevCL group did not report severe Bev-specific side effects or drug-related deaths.

There are a number of advantages of our study. We included elderly patients, patients with ECOG PS > 1, and patients with brain metastasis, who are usually excluded from prospective clinical trials. The selected concomitant regimens in our analysis reflect actual current real-world practice. Nevertheless, our study has several limitations, including its single-center, retrospective design. The sample size was relatively small to address controversy over the use of Bev beyond first PD. It is possible that oncologists' selection of treatment beyond first PD may have impacted the overall outcomes. For this reason, it is recommended that our study findings be combined with the results of controlled randomized clinical trials.

In summary, Bev continuation beyond PD after first-line treatment containing Bev did not improve survival in

patients with advanced NS-NSCLC. Further translational research into prognostic biomarkers for antiangiogenic treatment is needed to identify the patients that can really benefit from long-term inhibition of angiogenesis.

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Disclosure

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