

Bevacizumab with Single-agent Chemotherapy in Previously Treated Non-squamous Non-small-cell Lung Cancer: Phase II Study

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Abstract. *Aim: This study was designed to evaluate the efficacy and tolerability of bevacizumab with docetaxel or pemetrexed in previously treated patients with non-squamous non-small cell lung cancer. Patients and Methods: This study enrolled patients who had received at least one chemotherapy regimen, regardless of prior use of bevacizumab. Combinations of docetaxel or pemetrexed were chosen by attending physicians. The primary endpoint was progression-free survival, and secondary endpoints were safety, disease control rate, and overall survival. Results: Thirty patients from two institutions were eligible. The median progression-free and overall survival were 5.0 months (95% confidence interval=3.2-8.8 months) and 15.8 months (95% confidence interval=10.5-19.6 months), respectively. The disease control rate was 66.7%. Treatments were well tolerated, but the development rate of osteonecrosis of the jaw was 10%. Conclusion: Addition of bevacizumab in a salvage setting might be effective, but the development of osteonecrosis of the jaw needs to be monitored.*

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Lung cancer is a leading cause of cancer-related death worldwide, and non-small cell lung cancer (NSCLC), which accounts for approximately 85% of cases, is the major histological subtype (1). Recently, NSCLC was histologically divided into two subgroups, squamous cell and non-squamous (NSq) cell, because of different treatment strategies (2, 3). In patients with NSqNSCLC, docetaxel or pemetrexed are standard cytotoxic chemotherapies in the second-line setting (2-4).

Bevacizumab, which is approved for advanced NSqNSCLC, is a humanized monoclonal antibody that targets circulating vascular endothelial growth factor (VEGF)-A. In the first-line setting, the E4599 study showed that addition of bevacizumab to carboplatin and paclitaxel demonstrated longer overall survival (OS) and higher response rate in patients with NSqNSCLC compared to carboplatin and paclitaxel alone, which is the standard first-line chemotherapy regimen for patients with NSCLC (5). Previous studies also showed that as second-line treatment the addition of bevacizumab to single-agent chemotherapies, such as docetaxel or pemetrexed, has a good tolerability and potentially prolongs progression-free survival (PFS) and OS (6-9). Additionally, in patients with metastatic colorectal cancer who had previously received bevacizumab-containing therapy, continuation of bevacizumab beyond progression is the standard treatment strategy to improve OS (10). However, in patients with advanced NSqNSCLC, the efficacy and tolerability of bevacizumab-containing regimens as salvage therapies, especially in third-line settings or beyond, are not sufficient.

In this study, we hypothesized that bevacizumab-containing therapy in salvage settings may show clinical benefit for patients with NSqNSCLC, regardless of the treatment line.

This study was, therefore, designed to evaluate the efficacy and tolerability of bevacizumab in combination with docetaxel or pemetrexed, chosen by the attending physicians based on previous treatment, in patients with NSqNSCLC who were previously treated with at least one chemotherapy.

Patients and Methods

Study design. This multicenter phase II trial was conducted to evaluate the efficacy and tolerability of BEV in combination with docetaxel or pemetrexed in patients with NSqNSCLC previously treated with at least one chemotherapy. The primary endpoint was PFS, and the secondary endpoints were disease control rate (DCR), OS, and safety. This study was approved by the Ethics Committee of Hiroshima University Hospital on February 1, 2012 and was also approved by the institutional Ethics Committee of each participating institution. All participants provided written informed consent. This study was also registered with the University Hospital Medical Information Network (UMIN) Clinical Trial Registry system (trial number UMIN000007123).

Eligibility. All patients were diagnosed with NSqNSCLC by histological/cytological examinations. Each patient was required to meet the following criteria: (i) clinical stage IIIB, IV, or postoperative recurrence; (ii) progression during or after prior chemotherapy, including adjuvant therapy and tyrosine kinase inhibitors; (iii) Eastern Cooperative Oncology Group performance status (PS) of 0-2; (iv) age >20 years; (v) appropriate organ function (neutrophils >2,000 mm³, hemoglobin >9.0 g/dl, platelets >100,000/mm³, total bilirubin <1.5 mg/dl, aspartate aminotransferase <100 IU/l, alanine aminotransferase <100 IU/l, serum creatinine <1.5 mg/dl, urine dipstick for proteinuria <1+; (vi) life expectancy longer than 12 weeks. The main exclusion criteria included hemoptysis and bleeding diatheses, such as intratumoral cavitation and major blood vessel involvement. Patients receiving therapeutic anticoagulation drugs were also excluded.

Study treatment. The dose of bevacizumab in this study was 15 mg/kg administered by intravenous infusion on day 1 every 3 weeks, until progressive disease or unacceptable toxicity was observed. For combination chemotherapy regimens, pemetrexed or docetaxel was chosen by the physician based on prior therapies. Pemetrexed was administered intravenously over 10 minutes at a dose of 500 mg/m², and docetaxel was administered intravenously over 60 minutes at a dose of 60 mg/m² after bevacizumab on the same day. Salvage regimens were not restricted for each patient after discontinuation of protocol therapy.

Study assessments. Patients underwent tumor assessments at baseline and every 6 weeks using Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 (11). Adverse effects (AEs) were recorded using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (NCI-CTCAE v4.0) (12).

Statistical methods. In light of previous data (6-9), it was assumed that a median PFS of 4.5 months would indicate the potential usefulness of this treatment, whereas one of 3.8 months would be the lower limit of interest. Based on this assumption, the number of patients needed to evaluate the PFS data under 80% power for a one-sided error rate of 0.10 was calculated to be 28. Taking

Table I. Baseline characteristics of patients with non-squamous non-small-cell lung cancer treated with bevacizumab in combination with docetaxel or pemetrexed.

Variable	All patients	Treatment line (cytotoxic chemotherapy)	
		Second-line (n=19)	Third line or later (n=11)
Age, years			
Mean±SD	64.4±9.8	65.2±9.7	63.0±10.1
Gender			
Male/female	17/13	10/9	7/4
Performance status, n			
0/1/2	21/9/0	13/6/0	8/3/0
Stage, n			
IIIB/IV/recurrence	3/20/7	0/16/3	3/4/4
Histological subtype, n			
Ad/Pleo	29/1	18/1	11/0
Smoking history, pack-years			
Mean±SD	29.6±29.3	34.5±34.7	22.1±17.0
Hypertension, n			
Yes/no	7/23	3/16	4/7
Brain metastases, n			
Yes/no	12/18	9/10	3/8
Prior use of Bevacizumab, n			
Yes/no	18/12	11/8	7/4
Treatment line (only cytotoxic), n			
2/3/4 or more	19/6/5	19/0/0	0/6/5
EGFR mutation, n			
Yes/no	6/24	4/15	2/9
ALK rearrangement, n			
Yes/no/unknown	2/19/9	1/11/7	1/8/2
Cytotoxic drug, n			
Docetaxel/pemetrexed	25/5	15/4	10/1

Ad, Adenocarcinoma; ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; Pleo, pleomorphic carcinoma.

ineligible patients into account, the total sample size of this study was set at 35. Efficacy and safety analyses were planned for patients who received at least one dose of treatment. PFS and OS were analyzed using the Kaplan–Meier method to estimate median values with 95% confidence interval (CI). The DCR and the frequency of AEs were calculated. The relative dose intensity (RDI) of chemotherapy was calculated as follows: [Total administered dose of drug (mg)/total treatment duration (weeks)]/[total planned dose of drug (mg)/total planned duration (weeks)]. All statistical analyses were performed using JMP statistical software version 11.2.1 (SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics. This trial was terminated due to the results of the REVEL and AvaALL trials (13,14). Between September 2012 and July 2016, 31 patients were enrolled into

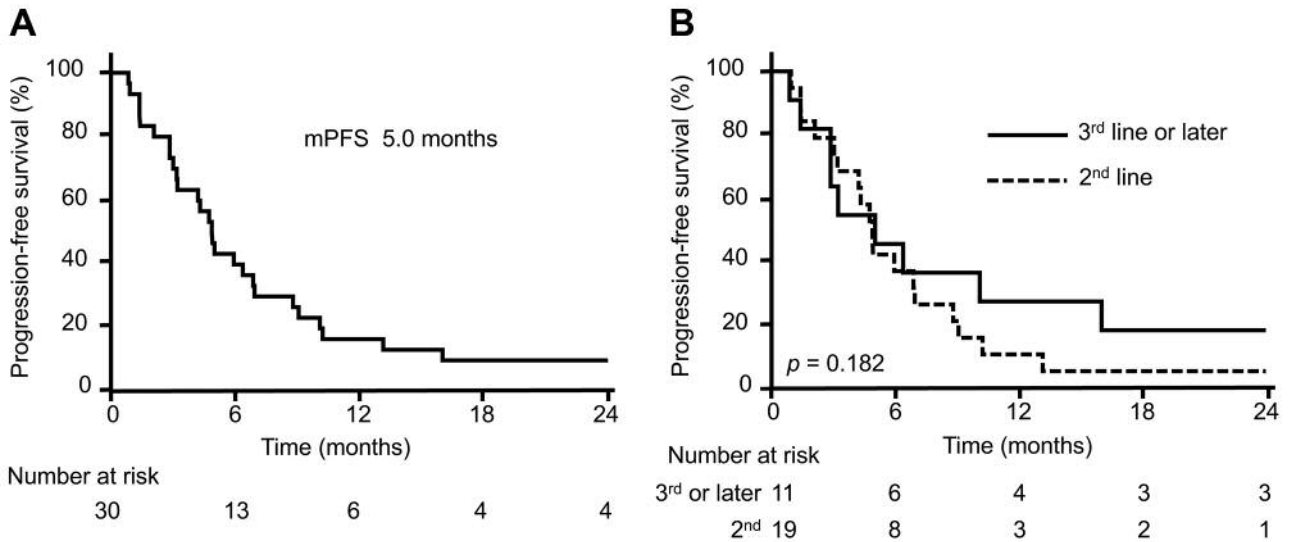


Figure 1. Kaplan–Meier analysis showing progression-free survival (PFS) for patients with non-squamous non-small-cell lung cancer treated with bevacizumab in combination with docetaxel or pemetrexed. The median PFS (mPFS) was 5.0 months [95% confidence interval (CI)=3.2-8.8 months] (A), and there was no significant difference in PFS between patients treated in the second-line (mPFS=6.4 months, 95% CI=1.4-16.1 months) and third-line setting or later (mPFS=4.9 months, 95% CI=3.0-7.0 months) (B).

this study from two participating hospitals, although one patient had not received protocol therapy. Ultimately, efficacy and safety were analyzed for 30 patients, and the sample size was large enough to provide statistical power. The patient characteristics are shown in Table I. Eight patients had epidermal growth factor receptor (*EGFR*) mutation- or anaplastic lymphoma kinase (*ALK*) rearrangement-positive NSqNSCLC and received at least one tyrosine kinase inhibitor before protocol therapy. When the treatment line was denoted, only cytotoxic regimens were counted (Table I). All patients were treated with platinum-based chemotherapy before protocol therapy. Nineteen out of the 30 patients were treated with protocol therapy as second-line cytotoxic chemotherapy, and the other 11 patients were treated with third-line or later regimens. Additionally, twenty-five out of the 30 patients were treated with docetaxel in combination with bevacizumab, and the other 5 patients were treated with pemetrexed in combination with bevacizumab. The data cut-off date was October 30, 2017.

Efficacy. The median follow-up period was 15.8 months (range=3.3-52.3 months). The 30 patients received a total of 228 cycles (median=5; range=1-25), and 27 of the patients died, while three remained alive. The median PFS was 5.0 months (95% CI=3.2-8.8 months), which was the primary endpoint (Figure 1A). The median survival time was 15.8 months (95% CI=10.5-19.6 months) (Figure 2) and the DCR was 66.7% (Table II).

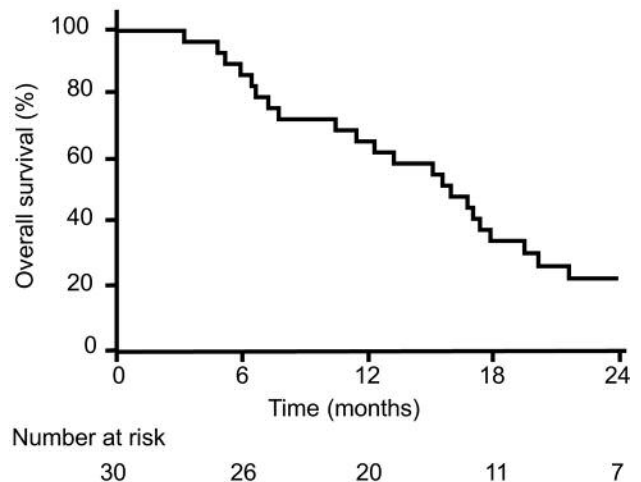


Figure 2. Kaplan–Meier analysis showing overall survival for patients with non-squamous non-small-cell lung cancer treated with bevacizumab in combination with docetaxel or pemetrexed. The median survival duration was 15.8 months (95% confidence interval=10.5-19.6 months).

The RDI of bevacizumab and the cytotoxic drugs docetaxel and pemetrexed were subsequently evaluated. The RDI of bevacizumab was 97.5±5.4%, and that of cytotoxic drugs was 86.3±16.7%. There was no significant difference in PFS, DCR, and RDI between the patients treated with

Table II. Summary of treatments of patients with non-squamous non-small-cell lung cancer in this study.

Variable	All patients	Treatment line (cytotoxic chemotherapy)	
		Second-line	Third-line or later
Best response			
PR/SD/PD/NE	9/11/6/4	7/6/5/1	2/5/1/3
DCR, %	66.7	68.4	63.6
Number of cycles			
Median (range)	5 (1-25)	5 (1-20)	4 (1-25)
RDI (cytotoxic drug), %			
Mean±SD	86.3±16.7	84.8±18.0	88.7±14.8
RDI (bevacizumab), %			
Mean±SD	97.5±5.4	97.0±6.3	98.5±3.3

DCR, Disease control rate; NE, not evaluated; PD, progressive disease; PR, partial response; RDI, relative dose intensity, SD, stable disease.

protocol therapy in the second-line setting and those treated in the third-line or later setting (Figure 1B and Table II).

Toxicity. AEs of any grade that occurred in at least 10% of the patients are shown in Table III. Treatments were well-tolerated, although the patients in this study included heavily pre-treated individuals. Hematological AEs of grade 3 or worse that occurred in at least 10% of the patients were leukopenia and neutropenia. The frequencies of hematological AEs tended to be higher in patients treated in the third-line setting or later compared to those treated in the second-line setting. Non-hematological AEs of grade 3 or worse that occurred in at least 10% of the patients were mucosal inflammation and febrile neutropenia. Remarkably, osteonecrosis of the jaw (ONJ) occurred in three out of the 30 patients, who were also treated with bone-modifying agents (BMA), including bisphosphonate and denosumab after dental screening and appropriate dental measures. All three of these patients were treated with the protocol therapy over 18 times, and their PFS was over 1 year (Table IV).

Discussion

This multicenter phase II trial was conducted to evaluate the clinical efficacy and toxicity of bevacizumab in combination with docetaxel or pemetrexed as salvage therapy for patients with NSqNSCLC, and the protocol therapy demonstrated median PFS of 5.0 months, median survival time 15.8 of months, and DCR of 66.7%. Overall toxicity was acceptable, although 10% of patients suffered from development of ONJ.

This study demonstrated the clinical efficacy of bevacizumab in combination with pemetrexed or docetaxel as

salvage therapy for patients with NSqNSCLC. Exploratory analysis also showed that the efficacy was similar for patients treated in the second-line setting and those treated in the third-line or later, potentially because there were no significant differences in age, PS, prior use of bevacizumab, and RDIs of protocol therapy between these two groups. Several studies have reported that bevacizumab combined with docetaxel or pemetrexed in the second-line setting showed clinical efficacy in patients with NSqNSCLC and achieved a median PFS range of 3.9-4.8 months (6-9). In 28 previously treated bevacizumab-naïve patients with NSqNSCLC, including 12 patients treated in the third-line setting or later, which is similar to our study cohort, Ohyanagi *et al.* reported that the median PFS of patients treated with bevacizumab combined with docetaxel was 7.2 months (15). These data suggest that bevacizumab-containing regimens as salvage therapy might have clinical benefit for patients with previously treated NSqNSCLC, regardless of the treatment line.

This study also showed that addition of bevacizumab to docetaxel or pemetrexed in the salvage line was tolerable, although AEs, especially leukopenia, neutropenia and febrile neutropenia, tended to be frequent in patients treated in the third-line setting or later. It should be noted that ONJ developed in three out of the 30 patients (10%), who also received BMA such as bisphosphonate and denosumab, after maximum precautions were taken that included dental screening and appropriate dental measures. Controversially, the combination of bevacizumab and BMA potentially increases the rate of ONJ development (16, 17), although the rate of 10% in this study was very high compared to the rates of 0.017-6.7% that were reported by previous studies evaluating the risk of ONJ with bevacizumab with/without BMA (16). One possibility explaining this is that the long-term use of bevacizumab might increase the risk of ONJ, because the three patients suffering from ONJ received bevacizumab for more than 1 year as salvage therapy. Further investigations are needed to evaluate whether the duration of bevacizumab administration and the combination of bevacizumab and BMA increase the risk of ONJ.

This study was terminated before complete patient accrual because of the results of four important clinical trials. Docetaxel or pemetrexed monotherapy was a standard regimen as second-line chemotherapy for patients with NSqNSCLC before beginning this study (2-4). However, after this study began, the REVEL trial showed that ramucirumab, which is an antibody to VEGF receptor 2, in combination with docetaxel as second-line treatment significantly improved OS in patients with NSCLC compared to docetaxel monotherapy (13). The CheckMate 057 (18) and KEYNOTE-010 (19) studies also showed that an antibody to programmed death-1 as second-line treatment significantly prolonged OS in patients with NSqNSCLC compared to docetaxel monotherapy (18, 19). Therefore, new

Table III. Adverse events occurring in at least 10% of patients with non-squamous non-small-cell lung cancer treated with bevacizumab in combination with docetaxel or pemetrexed.

	Treatment line (cytotoxic chemotherapy)					
	All patients (n=30) No. (%)		Second-line (n=19) No. (%)		Third-line or later (n=11) No. (%)	
	Any grade	>Grade 3	Any grade	>Grade 3	Any grade	>Grade 3
Hematological						
Leukopenia	26 (86.7)	15 (50.0)	16 (84.2)	8 (42.1)	10 (90.9)	7 (63.6)
Neutropenia	26 (86.7)	20 (66.7)	16 (84.2)	11 (57.9)	10 (90.9)	9 (81.8)
Anemia	14 (46.7)	2 (6.7)	9 (47.4)	1 (5.3)	5 (45.5)	1 (9.1)
Non-hematological						
Elevated AST	8 (26.7)	0 (0.0)	5 (26.3)	0 (0.0)	3 (27.3)	0 (0.0)
Elevated ALT	5 (16.7)	0 (0.0)	3 (15.8)	0 (0.0)	2 (18.2)	0 (0.0)
Increased creatinine	5 (16.7)	0 (0.0)	3 (15.8)	0 (0.0)	2 (18.2)	0 (0.0)
Diarrhea	6 (20.0)	0 (0.0)	2 (10.5)	0 (0.0)	4 (36.4)	0 (0.0)
Mucosal inflammation	11 (36.7)	3 (10.0)	6 (31.6)	2 (10.5)	5 (45.5)	1 (9.1)
Nausea	11 (36.7)	2 (6.7)	9 (47.4)	1 (5.3)	2 (18.2)	1 (9.1)
Vomiting	4 (13.3)	0 (0.0)	3 (15.8)	0 (0.0)	1 (9.1)	0 (0.0)
Fatigue	7 (23.3)	0 (0.0)	5 (26.3)	0 (0.0)	2 (18.2)	0 (0.0)
Pyrexia	8 (26.7)	0 (0.0)	6 (31.6)	0 (0.0)	2 (18.2)	0 (0.0)
Malaise	19 (63.3)	2 (6.7)	11 (57.9)	1 (5.3)	8 (72.7)	1 (9.1)
Pain	11 (36.7)	0 (0.0)	6 (31.6)	0 (0.0)	5 (45.5)	0 (0.0)
Anorexia	19 (63.3)	2 (6.7)	12 (63.2)	1 (5.3)	7 (63.6)	1 (9.1)
Rash	4 (13.3)	1 (3.3)	2 (10.5)	1 (5.3)	2 (18.2)	0 (0.0)
Peripheral neuropathy	8 (26.7)	1 (3.3)	5 (26.3)	1 (5.3)	3 (27.3)	0 (0.0)
Febrile neutropenia	8 (26.7)	8 (26.7)	4 (21.1)	4 (21.1)	4 (36.4)	4 (36.4)
Hypertension	6 (20.0)	2 (6.7)	4 (21.1)	1 (5.3)	2 (18.2)	1 (9.1)
Proteinuria	7 (23.3)	1 (3.3)	4 (21.1)	1 (5.3)	3 (27.3)	0 (0.0)
Hemorrhage	6 (20.0)	0 (0.0)	6 (31.6)	0 (0.0)	0 (0.0)	0 (0.0)
Osteonecrosis of the jaw	3 (10.0)	1 (3.3)	2 (10.5)	1 (5.3)	1 (9.1)	0 (0.0)

therapeutic regimens can be used to improve the OS of patients with NSqNSCLC in the salvage setting. Additionally, the AvaALL trial showed that continuous administration of bevacizumab in the second-line setting did not have any clinical benefit for patients with NSqNSCLC treated with priorly with bevacizumab (14). Based on these results, it was deemed that bevacizumab in combination with cytotoxic agents as salvage therapy was ethically unacceptable, and we believed that early termination of this study was appropriate.

In conclusion, addition of bevacizumab to single-agent chemotherapy might be a promising salvage treatment for patients with NSqNSCLC. While the toxicity of this treatment is acceptable, attention should be paid to the possible development of ONJ when BEV is administered as salvage therapy.

Acknowledgements

The Authors declare that they have no conflict of interest in regard to this study.

Table IV. Summary of characteristics of the three patients with osteonecrosis of the jaw after therapy with bevacizumab in combination with docetaxel or pemetrexed.

	Case 1	Case 2	Case 3
Gender	Male	Female	Female
Age, years	67	62	61
Performance status	1	1	0
Stage	IV	IV	IV
Treatment line	Second	Second	Third
Prior use of bevacizumab	No	Yes	Yes
Cytotoxic drug	DTX	DTX	DTX
<i>EGFR</i> mutation	Negative	Negative	Negative
<i>ALK</i> rearrangement	Unknown	Unknown	Negative
BMA	Zoledronic acid	Denosumab	Alendronic acid
CTCAE Grade of ONJ	Grade 2	Grade 3	Grade 2
Treatment cycle	18	25	20
Best response	PR	PR	SD
PFS, months	13.2	27.8	16.1

ALK, Anaplastic lymphoma kinase; BMA, bone-modifying agent; CTCAE, Common Terminology Criteria for Adverse Events; DTX, docetaxel; *EGFR*, epidermal growth factor receptor; ONJ, osteonecrosis of the jaw; PR, partial response; SD, stable disease.

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