ANTICANCER RESEARCH *40*: 2981-2987 (2020)
doi:10.21873/anticanres.14278

A Randomized Phase II Study of Maintenance Bevacizumab, Pemetrexed or Bevacizumab Plus Pemetrexed for Advanced Non-squamous Non-small Cell Lung Cancer

HIRONORI YOSHIDA[1], YOUNG HAK KIM[1], YUICHI SAKAMORI[2], HIROKI NAGAI[2], HIROAKI OZASA[1], TOSHIHIKO KANEDA[3,4], HIROSHIGE YOSHIOKA[3,5], HIROAKI NAKAGAWA[6], KEISUKE TOMII[7], ASUKA OKADA[8,9], KENICHI YOSHIMURA[10], MASATAKA HIRABAYASHI[1] and TOYOHIRO HIRAI[1]

[1]*Department of Respiratory Medicine, Graduate School of Medicine, Kyoto University, Kyoto, Japan;*
[2]*Department of Therapeutic Oncology, Graduate School of Medicine, Kyoto University, Kyoto, Japan;*
[3]*Department of Thoracic Oncology, Kansai Medical University Hospital, Hirakata, Japan;*
[4]*Department of Respiratory Medicine, Kobe City Medical Center West Hospital, Kobe, Japan;*
[5]*Department of Respiratory Medicine, Kurashiki Central Hospital, Kurashiki, Japan;*
[6]*Division of Respiratory Medicine, Department of Internal Medicine, Shiga University of Medical Science, Shiga, Japan;*
[7]*Department of Respiratory Medicine, Kobe City Medical Center General Hospital, Kobe, Japan;*
[8]*Department of Respiratory Medicine, Saiseikai Suita Hospital, Suita, Japan;*
[9]*Department of Medical Oncology, Osaka City General Hospital, Osaka, Japan;*
[10]*Center for Integrated Medical Research, Hiroshima University Hospital, Hiroshima University, Hiroshima, Japan;*
[11]*Department of Respiratory Medicine, Hyogo Prefectural Amagasaki General Medical Center, Amagasaki, Japan*

Abstract. *Background/Aim: Continuation maintenance therapy is standard for advanced nonsquamous non-small cell lung cancer; however, the optimal maintenance strategy has yet to be determined. Patients and Methods: Patients without disease progression after four cycles of carboplatin (CBDCA)+ pemetrexed (PEM)+ bevacizumab (BEV) were randomized to maintenance therapy with BEV, PEM, or BEV+PEM. The primary endpoint was 1-year progression-free survival (PFS) rate. Results: Of the 90 patients enrolled, 64 were randomly assigned to maintenance therapy. The 1-year PFS rate was 9.1% in the BEV arm, 19.1% in the PEM arm, and 19.1% in the BEV+PEM arm. The median PFS and overall survival (OS) were 4.0 and 43.1 months in the BEV arm, 4.5 and 32.0 months in the PEM arm, and 6.4 and 41.8 months in the BEV+PEM arm. Conclusion: The median PFS was numerically better in the BEV+PEM arm, but the median OS was not significantly different among the three arms.*

Correspondence to: Young Hak Kim, MD, Ph.D., Department of Respiratory Medicine, Graduate School of Medicine, Kyoto University, 54 Shogoin-Kawaharamachi, Sakyo-Ku, 606-8507 Kyoto, Japan. Tel: +81 757513830, Fax: +81 757514643, e-mail: ekim@kuhp.kyoto-u.ac.jp

Key Words: Maintenance therapy, nonsquamous non-small cell lung cancer, pemetrexed, bevacizumab, bevacizumab+pemetrexed.

Platinum-based chemotherapy provides survival benefits and better quality of life than palliative care alone as treatment for advanced non-small cell lung cancer (NSCLC) (1, 2). Pemetrexed (PEM), a multitargeted antifolate, demonstrated efficacy in combination with platinum agents for nonsquamous NSCLC (3). Furthermore, PEM as a maintenance therapy after platinum-based induction chemotherapy significantly improved survival compared with placebo in both continuation and switch maintenance settings (4, 5).

Bevacizumab (BEV) is another option for maintenance therapy. Combination chemotherapy of carboplatin (CBDCA), paclitaxel (PTX), and BEV followed by BEV maintenance (CPB) significantly improved the overall survival (OS) compared with CBDCA+PTX alone in patients with advanced nonsquamous NSCLC (6). A subsequent phase III study comparing CPB with CBDCA+PEM+BEV followed by BEV+PEM demonstrated similar efficacy and better tolerability for the latter arm (7). In addition, maintenance therapy using BEV+PEM significantly improved progression-free survival (PFS) compared with BEV alone after induction chemotherapy with cisplatin (CDDP)+PEM+BEV (8). Thus, three maintenance therapies, BEV alone, PEM alone, or BEV+PEM, after platinum-based

induction chemotherapy are currently available for nonsquamous NSCLC patients in clinical practice; however, the optimal maintenance strategy has yet to be determined.

For these reasons, we conducted a phase II study comparing BEV alone, PEM alone, and BEV+PEM following four cycles of induction chemotherapy with CBDCA+PEM+BEV in patients with advanced nonsquamous NSCLC.

Patients and Methods

Patient selection. Eligible patients had pathologically confirmed nonsquamous NSCLC with locally advanced stage IIIB, metastatic stage IV, or recurrent disease. Each patient was required to meet the following criteria: no prior chemotherapy; age 20-74 years; Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1; measurable lesions, and sufficient hematological, hepatic, and renal functions. Patients with active infection, uncontrollable diabetes mellitus or hypertension, severe cardiac condition, uncontrolled brain metastasis, intestinal bleeding, a history of major hemoptysis (≥2.5 ml red blood per episode), thrombotic or hemorrhagic disorder before registration, cavity lung lesions, tumors invading or abutting major blood vessels, myocardial infarction or cerebral infarction within 6 weeks, interstitial pneumonia or active lung fibrosis, effusion requiring drainage, recent major surgery within 4 weeks, palliative radiotherapy outside the thorax within 2 weeks or inside the thorax within 4 weeks before treatment, or active concomitant malignancy were excluded. After induction therapy, patients had to meet the following criteria for random assignment to maintenance therapy: completion of the defined induction therapy, no progressive disease [complete response (CR), partial response (PR), or stable disease (SD)] within 42 days from the start of the fourth cycle of prior chemotherapy, ECOG PS of 0 or 1, sufficient hematological, hepatic, and renal functions, and no pulmonary or other organ hemorrhage of grade 1 or less. The study protocol was approved by each participating institution's ethics review board. All patients provided written informed consent before treatment (Clinical trial registration: UMIN000006620).

Study design and treatment. Induction treatment, consisting of CBDCA (area under the curve of 6), PEM (500 mg/m^2), and BEV (15 mg/kg) on day 1, was initiated within 14 days from registration. Induction treatment was continued every three weeks for up to four cycles until disease progression or intolerable toxicities were observed. Patients who met the criteria were then randomly assigned at a 1:1:1 ratio to maintenance therapy with BEV (15 mg/kg), PEM (500 mg/m^2), or combination with BEV+PEM. Treatment cycles were repeated every three weeks until disease progression or intolerable toxicities were observed. Patients were stratified based on histology (adenocarcinoma *vs*. non-adenocarcinoma), the best response at the randomization (complete or partial response *vs*. stable disease), and epidermal growth factor receptor (EGFR) mutation status (yes *vs*. no or unknown).

Evaluation of tumor response and toxicity. Tumor response was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (9). Radiographic studies were performed to assess disease status every two cycles of chemotherapy for up to 1 year, and every three cycles thereafter. When the study therapy was discontinued for reasons other than disease progression, patients were evaluated every six weeks until disease progression. Post-discontinuation therapy use after maintenance therapy was at the discretion of the physician. All patients who received at least one cycle of chemotherapy were considered assessable for response evaluation.

Toxicity was evaluated based on the Common Terminology Criteria for Adverse Events, version 4.0. BEV was terminated if patients had grade 2 or higher hemorrhage or thromboembolic events, or gastrointestinal perforation. If toxicities persisted and patients did not meet the criteria for up to 14 and 21 days from the completion of the previous cycle of chemotherapy in the induction and maintenance phases, respectively, the study treatment was terminated. All patients who had received at least one dose of study treatment were included in the safety analysis.

Statistical analysis. In this multicenter, randomized, phase II study, the primary endpoint was the 1-year PFS rate in each maintenance therapy arm. The secondary endpoints were PFS, OS, and safety. PFS and OS were measured from the randomization and estimated using the Kaplan–Meier method. Patients who were lost to follow-up without events were censored at the last follow-up. Based on the Simon selection design, the number of patients was set to achieve a statistical power of 83% and 88%, with an expected 1-year PFS rate of 27.5% in the PEM arm, 30% in the BEV+PEM arm, and a threshold rate of 15% in the BEV arm. The targeted sample size was 33 in each maintenance group. All analyses were performed using JMP 14 software (SAS Institute, Cary, NC, USA).

Results

Patient characteristics. Between March 2012 and February 2017, 90 patients were enrolled at 11 medical centers in Japan (Figure 1). The baseline characteristics are listed in Table I. The median age was 66 years (range=39-74 years), 31 (34%) patients were female, and 25 (28%) were never smokers. Adenocarcinoma was the most common histology (94%). Twenty-six (29%) and 22 (24%) patients had EGFR mutations and brain metastases, respectively.

After induction therapy, 64 (71%) patients were randomly assigned to maintenance therapy: 22 to BEV, 21 to PEM, and 21 to BEV+PEM arms. The baseline characteristics were balanced among the three arms, but the number of patients with brain metastasis was smaller in the BEV+PEM arm (Table I).

Treatment. All eligible patients received induction chemotherapy (Figure 1). The reasons for induction treatment discontinuation were disease progression (13 patients), toxicity (8 patients), and other (5 patients). All randomized patients received maintenance therapy. The median number of maintenance therapy cycles was 4 (range=2-19) in the BEV arm, 6 (range=2-39) in the PEM arm, and 4 (range=1-25) in the BEV+PEM arm. Among the randomized patients, the most common reason for maintenance treatment discontinuation was disease progression. As of the cut-off date of August 10th, 2019, all enrolled patients had discontinued maintenance therapy. This study was terminated due to slow patient accrual.

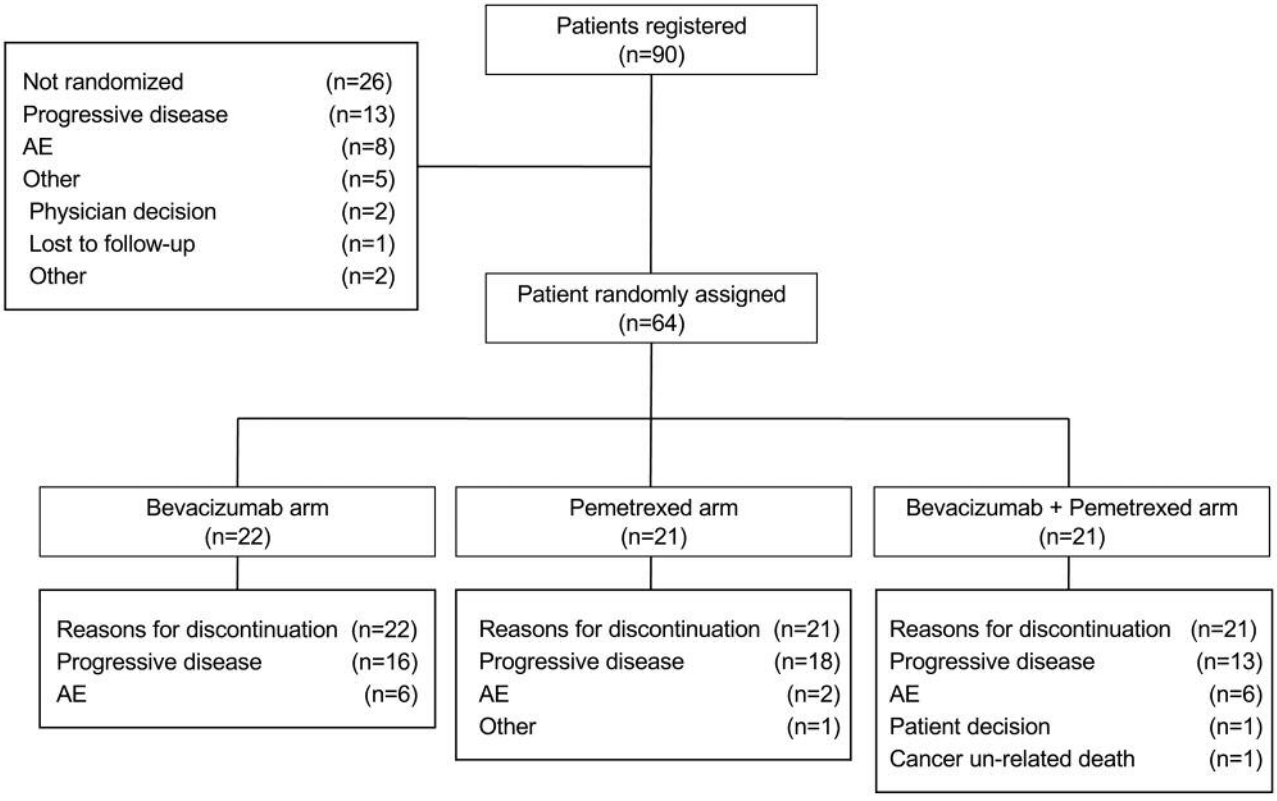

Figure 1. *Study profile. AE: Adverse event.*

Efficacy. In the induction phase, disease control was confirmed in 83% of patients (75 of 90), with 51(57%) patients achieving PR and 24 (27%) having SD. At the cut-off date, 36 (40%) of 90 patients were alive. The median follow-up period after randomization was 31.6 [95% confidence interval (CI)=26.4-37.8] months. The 1-year PFS rate was 9.1% (95%CI=2.5-27.8) in the BEV arm, 19.1% (95%CI=7.7-40.0) in the PEM arm, and 19.1% (95%CI=7.7-40.0) in the BEV+PEM arm (BEV *vs.* PEM: p=0.35, BEV *vs.* BEV+PEM: p=0.35). The median PFS was 4.0 (95%CI=2.8-5.7) months in the BEV arm, 4.5 (95%CI=3.3-8.4) months in the PEM arm, and 6.4 (95%CI=2.1-8.7) months in the BEV+PEM arm (BEV *vs.* PEM: hazard ratio (HR) 0.62 (95%CI=0.32-1.18); p=0.14, BEV *vs.* BEV+PEM: HR 0.61 (95%CI=0.32-1.17); p=0.13) (Figure 2A). The median OS was 43.1 [95%CI, 16.2-not reached (NR)] months in the BEV arm, 32.0 (95%CI= 21.3-65.1) months in the PEM arm, and 41.8 (95%CI=11.8-NR) months in the BEV+PEM arm [BEV *vs.* PEM: HR 1.41 (95%CI=0.59-3.38); p=0.40, BEV *vs.* BEV+PEM: HR 1.12 (95%CI=0.49-2.58); p=0.78] (Figure 2B).

Safety. During the induction phase, grade 3 and 4 adverse events (AEs) were observed in 39% and 11% of patients, respectively. The most common grade ≥3 AEs (in >5%) were neutropenia (28%), thrombocytopenia (18%), and anemia (10%). During the maintenance phase, most AEs reported were grade 1 or 2 (Table II). Grade ≥3 AEs were observed in 18% in the BEV arm, 33% in the PEM arm, and 33% in the BEV+PEM arm. The most common grade ≥3 AEs were hypertension (18%) in the BEV arm, and neutropenia in both the PEM (24%) and BEV+PEM arms (19%). AEs leading to maintenance treatment discontinuation were observed in 6 patients (6 with proteinuria) in the BEV arm, 2 patients (2 with increased creatinine) in the PEM arm, and 6 patients (3 with proteinuria, 1 with increased creatinine, 1 with stomatitis, and 1 with pneumonia) in the BEV+PEM arm. There were no treatment-related deaths.

Post-discontinuation therapy. Post-discontinuation therapy is described in Table III. As of the cut-off date, 22 (100%) patients in the BEV arm, 20 (95%) in the PEM arm, and 17 (81%) in the BEV+PEM arm had received subsequent post-discontinuation therapy. Among the EGFR mutation-positive patients, EGFR-tyrosine kinase inhibitors were administered to all 8 patients in the BEV arm, 7 of 8 patients in the PEM arm, and 7 of 8 patients in the BEV+PEM arm. The number of patients who received immune checkpoint inhibitors was

Table I. *Patient characteristics*.

	All patients (N=90)	BEV arm (N=22)	PEM arm (N=21)	BEV+PEM arm (N=21)
Median age (range), years	66 (39-74)	66 (40-74)	65 (55-74)	67 (39-73)
Gender				
Male	59	14	12	14
Female	31	8	9	7
PS				
0	60	13	16	18
1	30	9	5	3
Disease stage				
IIIB	4	1	1	1
IV	83	19	20	20
Recurrent	3	2	0	0
Histology				
Adenocarcinoma	85	21	21	19
Large cell	3	1	0	1
NSCLC, NOS	2	0	0	1
Smoking status				
Never	25	7	10	5
Ever or current	65	15	11	16
EGFR mutation				
No	64	14	13	13
Yes	26	8	8	8
L858R or 19 deletion	25	8	7	8
Other	1	0	1	0
Brain metastases				
Yes	22	7	5	2
No	68	15	16	19
Best tumor response to induction therapy				
Complete or partial response	-	15	15	15
Stable disease	-	7	6	6

BEV: Bevacizumab; PEM: pemetrexed; PS: performance status; NSCLC: non-small cell lung cancer; NOS: not otherwise specified.

similar among the three arms: 6 in the BEV arm, 6 in the PEM arm, and 7 in the BEV+PEM arm.

Discussion

Maintenance therapy is a standard treatment for advanced nonsquamous NSCLC; however, the optimal maintenance therapy has yet to be determined. In this study, we compared three maintenance regimens, PEM alone, BEV alone, and BEV+PEM, in the continuation maintenance setting. The median PFS was numerically better in the BEV+PEM arm, but there was no significant difference in terms of the 1-year PFS rate or OS.

To date, there are reports that the addition of bevacizumab to single-agent chemotherapy tends to improve PFS in the second-line or later setting (10-12). In the maintenance setting, continuation maintenance regimens have been compared in several clinical trials. Maintenance therapy with BEV+PEM following induction chemotherapy with CDDP+PEM+BEV (AVAPERL) (8) or with CBDCA+PEM+BEV (WJOG5610L) (13) significantly improved the PFS compared with BEV alone; however, the OS was not significantly different between BEV+PEM and BEV alone in both studies. Recently, three maintenance therapies, BEV alone, PEM alone, and BEV+PEM, following induction chemotherapy with CBDCA+PTX+BEV were directly compared in the switch maintenance setting (ECOG-ACRIN 5508). Although maintenance therapy with BEV+PEM resulted in a significantly longer PFS than that with BEV alone or PEM alone, there was no significant OS difference among the three arms (14).

The impact of post-progression survival may explain these improvements in PFS but not in OS (15). Although details were not disclosed in the ECOG-ACRIN 5508 study, more than 70% and 80% of the patients received post-discontinuation therapy in the AVAPERL and WJOG5610L studies, respectively. Similarly, in our study, more than 80% of the patients received post-discontinuation therapy. These high rates of salvage treatment may have influenced the OS results, including in our study.

With the recent advent of immune checkpoint inhibitors (ICI), the combination of ICI with platinum-based chemotherapy has become the new standard treatment for

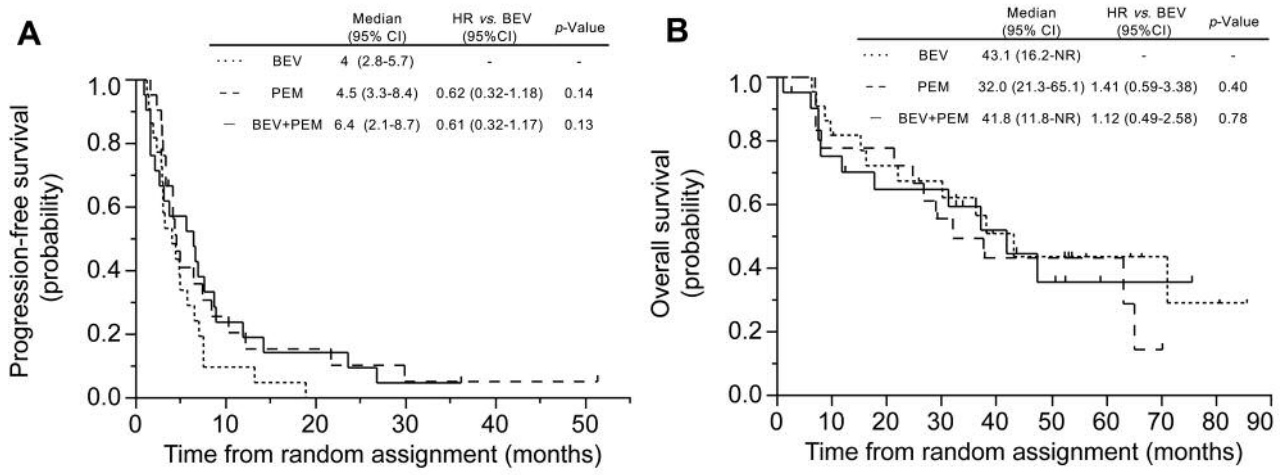

Figure 2. *Kaplan-Meier curves for progression-free survival (A) and overall survival (B) measured after randomization. HR: Hazard ratio; CI: confidence interval; BEV: bevacizumab; PEM: pemetrexed; NR: not reached.*

Table II. *Adverse events.*

	BEV arm (n=22)				PEM arm (n=21)				BEV+PEM arm (n=21)			
	Gr 1 or 2		Gr 3 or 4		Gr 1 or 2		Gr 3 or 4		Gr 1 or 2		Gr 3 or 4	
	n	%	n	%	n	%	n	%	n	%	n	%
Leukopenia	4	18	0	0	8	38	2	10	8	38	3	14
Neutropenia	3	14	0	0	5	24	5	24	7	33	4	19
Anemia	10	45	0	0	11	52	0	0	11	52	0	0
Thrombocytopenia	4	18	0	0	4	19	1	5	7	33	0	0
Creatinine	4	18	0	0	10	48	0	0	7	33	0	0
AST	6	27	0	0	15	71	0	0	13	62	0	0
ALT	2	9	0	0	8	38	0	0	10	48	0	0
Febrile neutropenia	0	0	0	0	0	0	0	0	0	0	0	0
Proteinuria	13	59	0	0	3	13	0	0	9	43	0	0
Fatigue	5	23	0	0	7	33	0	0	12	57	0	0
Nausea	1	5	0	0	6	29	0	0	6	29	0	0
Vomiting	0	0	0	0	1	5	0	0	2	10	0	0
Edema	0	0	0	0	3	14	0	0	0	0	0	0
Neuropathy, sensory	3	14	0	0	1	5	0	0	1	5	0	0
Mucositis	1	5	0	0	5	24	0	0	4	19	0	0
Anorexia	2	9	0	0	1	5	0	0	9	43	1	5
Diarrhea	1	5	0	0	1	5	0	0	2	10	0	0
Constipation	3	14	0	0	4	19	0	0	0	0	0	0
Rash	2	9	0	0	1	5	0	0	2	10	0	0
Thromboembolic event	0	0	0	0	0	0	1	5	0	0	0	0
Hypertension	6	27	4	18	5	24	1	5	7	33	0	0
Epistaxis	4	18	0	0	2	10	0	0	5	24	0	0
Pneumonitis	0	0	0	0	0	0	0	0	0	0	1	5

BEV: Bevacizumab; PEM: pemetrexed; AST: aspartate aminotransferase; ALT: alanine aminotransferase.

NSCLC in the first-line setting, and continuation maintenance either with PEM alone or BEV alone in combination with ICI is standard for patients with nonsquamous NSCLC (16, 17). Maintenance therapy with BEV+PEM in combination with ICI may be more promising because several preclinical studies have suggested that BEV (18, 19) and PEM (20) affect the immune system through different mechanisms in the tumor microenvironment,

Table III. *Post-discontinuation therapy.*

	BEV arm (n=22)	PEM arm (n=21)	BEV+PEM (n=21)
No post-progression therapy, n (%)	0 (0)	1 (5)	4 (19)
2nd-line therapy, n (%)	22 (100)	20 (95)	17 (81)
EGFR-TKI	8	6	7
Taxanes	9	8	6
PEM	1	0	0
ALK-TKI	3	1	0
Platinum-based	0	1	0
ICI	1	1	1
Others	0	1	3
Unknown	0	2	0
3rd-line therapy, n (%)	17 (77)	15 (71)	11 (52)
EGFR-TKI	3	2	4
Taxanes	3	6	2
PEM	0	1	0
Platinum-based	2	1	0
ICI	2	2	4
Others	7	3	1
4th-line therapy	11 (50)	12 (57)	6 (29)
EGFR-TKI	2	1	2
Taxanes	4	4	2
PEM	0	2	0
Platinum-based	2	1	0
ICI	0	3	1
Others	3	1	1

BEV: Bevacizumab; PEM: pemetrexed; EGFR: epidermal growth factor receptor; TKI: tyrosine kinase inhibitor; ALK: anaplastic lymphoma kinase; ICI: immune checkpoint inhibitor.

resulting in anti-tumor immune response leading to clinical efficacy. Further studies are warranted to determine the maintenance strategy in the ICI era.

Conclusion

This was the first study comparing three continuation maintenance strategies for nonsquamous NSCLC patients following CBDCA+PEM+BEV. The median PFS was numerically better in the BEV+PEM arm, but the median OS was not significantly different among the three arms.

Conflicts of Interest

Y.H.K. received honoraria from Chugai Pharmaceutical Co. Ltd. H.Y. received honoraria from Eli Lilly Japan K.K. and Chugai Pharmaceutical Co. Ltd during the study, and honoraria from AstraZeneca K.K., Boehringer Ingelheim Japan Inc., Bristol-Myers Squibb Co. Ltd., Ono Pharmaceutical Co. Ltd., Kyowa Hakko Kirin Co. Ltd., MSD K.K., Delta fly pharma, and Taiho Pharmaceutical Co. Ltd. outside of the submitted work. T.K. served as an advisory board member of Eli Lilly Japan K.K. outside of the submitted work. T.H. received grants from Chugai Pharmaceutical Co. Ltd. outside of the submitted work. All remaining Authors have declared no conflicts of interest.

Authors' Contributions

Y.H.K. designed the study. H.Y., Y.H.K., Y.S., H.N., H.O., T.K., H.Y., H.N., K.T., A.O., and M.H. contributed to data collection. H.Y., K.Y., and Y.H.K. contributed to the analysis and interpretation of data. H.Y. drafted and revised the manuscript; T.H. and Y.H.K. supervised the study and revised the manuscript. All Authors reviewed the manuscript.

References

1 NSCLC Meta-Analyses Collaborative Group: Chemotherapy in addition to supportive care improves survival in advanced non-small-cell lung cancer: a systematic review and meta-analysis of individual patient data from 16 randomized controlled trials. J Clin Oncol *26(28)*: 4617-4625, 2018. PMID: 18678835. DOI: 10.1200/JCO.2008.17.7162

2 Non-Small Cell Lung Cancer Collaborative Group: Chemotherapy and supportive care versus supportive care alone for advanced non-small cell lung cancer. Cochrane Database Syst Rev *(5)*: CD007309, 2010. PMID: 20464750. DOI: 10.1002/14651858.CD007309.pub2

3 Scagliotti GV, Parikh P, von Pawel J, Biesma B, Vansteenkiste J, Manegold C, Serwatowski P, Gatzemeier U, Digumarti R, Zukin M, Lee JS, Mellemgaard A, Park K, Patil S, Rolski J, Goksel T, de Marinis F, Simms L, Sugarman KP and Gandara D: Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. J Clin Oncol *26(21)*: 3543-3551, 2008. PMID: 18506025. DOI: 10.1200/JCO.2007.15.0375

4 Paz-Ares L, de Marinis F, Dediu M, Thomas M, Pujol JL, Bidoli P, Molinier O, Sahoo TP, Laack E, Reck M, Corral J, Melemed S, John W, Chouaki N, Zimmermann AH, Visseren-Grul C and Gridelli C: Maintenance therapy with pemetrexed plus best supportive care versus placebo plus best supportive care after induction therapy with pemetrexed plus cisplatin for advanced non-squamous non-small-cell lung cancer (PARAMOUNT): a double-blind, phase 3, randomised controlled trial. Lancet Oncol *13(3)*: 247-255, 2012. PMID: 22341744. DOI: 10.1016/S1470-2045(12)70063-3

5 Ciuleanu T, Brodowicz T, Zielinski C, Kim JH, Krzakowski M, Laack E, Wu YL, Bover I, Begbie S, Tzekova V, Cucevic B, Pereira JR, Yang SH, Madhavan J, Sugarman KP, Peterson P, John WJ, Krejcy K and Belani CP: Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomised, double-blind, phase 3 study. Lancet *374(9699)*: 1432-1440, 2009. PMID: 19767093. DOI: 10.1016/S0140-6736(09)61497-5

6 Sandler A, Gray R, Perry MC, Brahmer J, Schiller JH, Dowlati A, Lilenbaum R and Johnson DH: Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med *355(24)*: 2542-2550, 2006. PMID: 17167137. DOI: 10.1056/NEJMoa061884

7 Patel JD, Socinski MA, Garon EB, Reynolds CH, Spigel DR, Olsen MR, Hermann RC, Jotte RM, Beck T, Richards DA, Guba SC, Liu J, Frimodt-Moller B, John WJ, Obasaju CK, Pennella EJ, Bonomi P and Govindan R: PointBreak: a randomized phase III study of pemetrexed plus carboplatin and bevacizumab followed by maintenance pemetrexed and bevacizumab versus paclitaxel plus carboplatin and bevacizumab followed by maintenance

bevacizumab in patients with stage IIIB or IV nonsquamous non-small-cell lung cancer. J Clin Oncol *31(34)*: 4349-4357, 2013. PMID: 24145346. DOI: 10.1200/JCO.2012.47.9626

8 Barlesi F, Scherpereel A, Rittmeyer A, Pazzola A, Ferrer Tur N, Kim JH, Ahn MJ, Aerts JG, Gorbunova V, Vikström A, Wong EK, Perez-Moreno P, Mitchell L and Groen HJ: Randomized phase III trial of maintenance bevacizumab with or without pemetrexed after first-line induction with bevacizumab, cisplatin, and pemetrexed in advanced nonsquamous non-small-cell lung cancer: AVAPERL (MO22089). J Clin Oncol *31(24)*: 3004-3011, 2013. PMID: 23835708. DOI: 10.1200/JCO.2012.42.3749

9 Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D and Verweij J: New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 45(2): 228-247, 2009. PMID: 19097774. DOI: 10.1016/j.ejca.2008.10.026

10 Herbst RS, O'Neill VJ, Fehrenbacher L, Belani CP, Bonomi PD, Hart L, Melnyk O, Ramies D, Lin M and Sandler A: Phase II study of efficacy and safety of bevacizumab in combination with chemotherapy or erlotinib compared with chemotherapy alone for treatment of recurrent or refractory non-small cell lung cancer. J Clin Oncol *25(30)*: 4743-4750, 2007. PMID: 17909199. DOI: 10.1200/JCO.2007.12.3026

11 Adjei AA, Mandrekar SJ, Dy GK, Molina JR, Adjei AA, Gandara DR, Ziegler KL, Stella PJ, Rowland KM Jr, Schild SE and Zinner RG: Phase II trial of pemetrexed plus bevacizumab for second-line therapy of patients with advanced non-small-cell lung cancer: NCCTG and SWOG study N0426. J Clin Oncol *28(4)*: 614-619, 2010. PMID: 19841321. DOI: 10.1200/JCO.2009.23.6406

12 Yamaguchi K, Masuda T, Fujitaka K, Miwata K, Sakamoto S, Horimasu Y, Hamai K, Miyamoto S, Nakashima T, Okamoto Y, Iwamoto H, Ishikawa N, Miyata Y, Okada M, Hamada H and Hattori N: Bevacizumab with single-agent chemotherapy in previously treated non-squamous non-small-cell lung cancer: phase II study. In Vivo *32(5)*: 1155-1160, 2018. PMID: 30150438. DOI: 10.21873/invivo.11358

13 Seto T, Azuma K, Yamanaka T, Sugawara S, Yoshioka H, Wakuda K, Atagi S, Iwamoto Y, Hayashi H, Okamoto I, Saka H, Mitsuoka S, Fujimoto D, Nishino K, Horiike A, Daga H, Sone T, Yamamoto N, Nakagawa K and Nakanishi Y: Randomized phase III study of continuation maintenance bevacizumab with or without pemetrexed in advanced nonsquamous non-small-cell lung cancer: COMPASS (WJOG5610L). J Clin Oncol *38(8)*: 793-803, 2020. PMID: 31880966. DOI: 10.1200/JCO.19.01494

14 Ramalingam SS, Dahlberg SE, Belani CP, Saltzman JN, Pennell NA, Nambudiri GS, McCann JC, Winegarden JD, Kassem MA, Mohamed MK, Rothman JM, Lyss AP, Horn L, Stinchcombe TE and Schiller JH: Pemetrexed, bevacizumab, or the combination as maintenance therapy for advanced nonsquamous non-small-cell lung cancer: ECOG-ACRIN 5508. J Clin Oncol *37(26)*: 2360-2367, 2019. PMID: 31361535. DOI: 10.1200/JCO.19.01006

15 Broglio KR and Berry DA: Detecting an overall survival benefit that is derived from progression-free survival. J Natl Cancer Inst *101(23)*: 1642-1649, 2009. PMID: 19903805. DOI: 10.1093/jnci/djp369

16 Gandhi L, Rodríguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, Domine M, Clingan P, Hochmair MJ, Powell SF, Cheng SY, Bischoff HG, Peled N, Grossi F, Jennens RR, Reck M, Hui R, Garon EB, Boyer M, Rubio-Viqueira B, Novello S, Kurata T, Gray JE, Vida J, Wei Z, Yang J, Raftopoulos H, Pietanza MC and Garassino MC: Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. N Engl J Med *378(22)*: 2078-2092, 2018. PMID: 29658856. DOI: 10.1056/NEJMoa1801005

17 Socinski MA, Jotte RM, Cappuzzo F, Orlandi F, Stroyakovskiy D, Nogami N, Rodríguez-Abreu D, Moro-Sibilot D, Thomas CA, Barlesi F, Finley G, Kelsch C, Lee A, Coleman S, Deng Y, Shen Y, Kowanetz M, Lopez-Chavez A, Sandler A and Reck M: Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. N Engl J Med *378(24)*: 2288-2301, 2018. PMID: 29863955. DOI: 10.1056/NEJMoa1716948

18 Wallin JJ, Bendell JC, Funke R, Sznol M, Korski K, Jones S, Hernandez G, Mier J, He X, Hodi FS, Denker M, Leveque V, Cañamero M, Babitski G, Koeppen H, Ziai J, Sharma N, Gaire F, Chen DS, Waterkamp D, Hegde PS and McDermott DF: Atezolizumab in combination with bevacizumab enhances antigen-specific T-cell migration in metastatic renal cell carcinoma. Nat Commun *7*: 12624, 2016. PMID: 27571927. DOI: 10.1038/ncomms12624

19 Voron T, Colussi O, Marcheteau E, Pernot S, Nizard M, Pointet AL, Latreche S, Bergaya S, Benhamouda N, Tanchot C, Stockmann C, Combe P, Berger A, Zinzindohoue F, Yagita H, Tartour E, Taieb J and Terme M: VEGF-A modulates expression of inhibitory checkpoints on CD8+ T cells in tumors. J Exp Med *212(2)*: 139-148, 2015. PMID: 25601652. DOI: 10.1084/jem.20140559

20 Schaer DA, Geeganage S, Amaladas N, Lu ZH, Rasmussen ER, Sonyi A, Chin D, Capen A, Li Y, Meyer CM, Jones BD, Huang X, Luo S, Carpenito C, Roth KD, Nikolayev A, Tan B, Brahmachary M, Chodavarapu K, Dorsey FC, Manro JR, Doman TN, Donoho GP, Surguladze D, Hall GE, Kalos M and Novosiadly RD: The folate pathway inhibitor pemetrexed pleiotropically enhances effects of cancer immunotherapy. Clin Cancer Res *25(23)*: 7175-7188, 2019. PMID: 31409612. DOI: 10.1158/1078-0432.CCR-19-0433

Received April 4, 2020
Revised April 12, 2020
Accepted April 13, 2020