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ORIGINAL ARTICLE

Treatment with or without bevacizumab as a first-line and maintenance therapy for advanced non-squamous non-small cell lung cancer: A retrospective study

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Keywords
Antiangiogenic targeted therapy; chemotherapy; pemetrexed; progressive-free survival.

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Abstract

Background: Pemetrexed and bevacizumab as monotherapies, or in combination, have been approved for maintenance therapy following platinum-based induction in patients with advanced nonsquamous non-small cell lung cancer (NSCLC). The differences in the benefits of bevacizumab for treatment during early or late NSCLC have not yet been characterized.

Methods: We retrospectively analyzed data from 35 patients with advanced naïve NSCLC who had received pemetrexed/platinum with or without bevacizumab followed by maintenance therapy with pemetrexed alone or pemetrexed plus bevacizumab. The data were analyzed using the Kaplan-Meier method and Cox regression adjusted for risk factors. Patients were grouped according to treatment conditions. Group A received pemetrexed plus platinum followed by pemetrexed alone (Pem-Pt/Pem). Group B received pemetrexed plus platinum followed by pemetrexed and bevacizumab (Group B; Pem-Pt/Pem + Bev). Group C received pemetrexed, platinum, and bevacizumab during induction therapy, and pemetrexed as maintenance therapy (Group C; Pem-Pt + Bev/Pem + Bev). We assessed the significance of introduction of bevacizumab at different stages of treatment.

Results: A total of 13 (37.1%) patients were included in Group A, nine patients (25.7%) were included in Group B, and 13 patients (37.1%) were included in Group C. Among the 35 patients, 69.2% were male, and the median age was 59 years (range 40–75). The median progression-free survival (PFS) was 7.7 months (231 days, range 134–410 days) in Group A, 9.3 months (280 days, range 84–565 days) in Group B, and 8.0 months (241 days, range 108–665 days) in Group C. The median PFS was not significantly different among the three groups (P = 0.233). Similarly, bevacizumab did not significantly affect PFS (P = 0.630).

Conclusions: The addition of bevacizumab into induction chemotherapy or maintenance therapy provided limited benefits to PFS in our study, but previous studies suggested that bevacizumab may improve disease control. In that way, we presume that early use of bevacizumab may provide a greater benefit.

Introduction

Lung cancer is the most common cause of cancer-related death worldwide.[1] At the time of diagnosis, the majority of lung cancer cases are in advanced stages, resulting in a lack of curative treatment options. Fewer than 5% of patients with advanced lung cancer live for five years following diagnosis.[2] Non-small cell lung cancer (NSCLC) is the most frequent histologic type, and the nonsquamous histologic type is the predominant subtype. Targeted therapeutics and immunological checkpoint inhibitors[3] have been developed for the treatment of lung cancer. However, chemotherapy is the first choice for treatment of advanced NSCLC with wild-type driver genes or cases that do not

respond to immunotherapy. Therefore, efforts to improve therapeutic efficacy have focused primarily on development of novel agents or development of new treatment regimens.[4–6]

Many studies have shown that administration of bevacizumab[1, 6–15] with platinum chemotherapy significantly improved the objective response rate (ORR), progression-free survival (PFS), and overall survival (OS), compared to platinum-based chemotherapy alone. Moreover, use of bevacizumab[16–20] as a maintenance therapy has been shown to improve OS. The PARAMOUNT[21] and JMEN[22] studies showed that pemetrexed reduced the risk of disease progression and prolonged progressive-free survival as both a continued maintenance and a switch maintenance treatment. The AVAPERL (MO22089)[23] study showed that combination of continued maintenance treatment with bevacizumab and pemetrexed resulted in a PFS of 10.2 months. Based on these studies, the current National Comprehensive Cancer Network (NCCN 2019 V.6) guidelines[24] and the European Society of Medical Oncology guidelines[25] recommend pemetrexed/cisplatin or carboplatin plus bevacizumab as a first-line chemotherapy treatment, followed by pemetrexed monotherapy, bevacizumab monotherapy, or the combination of pemetrexed plus bevacizumab as continued maintenance therapies. Pemetrexed is the recommended switch maintenance therapy.

Different combinations of platinum-based chemotherapy may have contributed to significant heterogeneity of outcomes (complete remission, partial remission, or stable disease) among previous studies. Optimal timing for addition of bevacizumab has not been characterized. In this study, we evaluated the efficacy of introducing bevacizumab at different points (during induction of therapy or as maintenance therapy).

Methods

Patient inclusion data

We retrospectively reviewed the medical records of patients with advanced NSCLC who had received pemetrexed/platinum (cisplatin or carboplatin) between April 2016 and September 2018 at the Respiratory Department of Peking Union Medical College Hospital, Beijing, China. The inclusion criteria were as follows: (i) histologically or cytologically confirmed advanced unresectable (stage IV) nonsquamous (non-SQ) NSCLC; (ii) received pemetrexed-platinum (cisplatin or carboplatin) as the first-line treatment for four cycles and pemetrexed as maintenance therapy, received pemetrexed-platinum (cisplatin or carboplatin) as the first-line treatment for four cycles and pemetrexed plus bevacizumab as maintenance therapy, or received pemetrexed-platinum (cisplatin or carboplatin) plus bevacizumab as the first-line treatment for four cycles and pemetrexed plus bevacizumab as maintenance therapy; (iii) achieved partial remission or stable disease following four cycles of induction chemotherapy; and (iv) availability of the following baseline information: sex, age, Eastern Cooperative Oncology Group-Performance Status (ECOG-PS), staging (UICC classification, eighth edition), smoking status, and adverse events.

The study protocol was approved by the institutional ethics review board prior to initiation of the study. Patients and physicians were required to provide written consent to release information prior to data collection.

Treatment and data collection

The patients were divided into three groups based on their first-line and maintenance therapies. The first group of patients (Pem-Pt/Pem) received a pemetrexed-platinum regimen as the first-line chemotherapy for four cycles and pemetrexed as maintenance therapy. The second group of patients (Pem-Pt /Pem + Bev) received pemetrexed-platinum for four cycles and pemetrexed plus bevacizumab maintenance therapy. The third group of patients (Pem-Pt + Bev/ Pem + Bev) received pemetrexed and platinum plus bevacizumab for four cycles and pemetrexed plus bevacizumab as maintenance therapy.

Treatments consisted of platinum (cisplatin 75 mg/m^2 or carboplatin at target AUC = 5) and pemetrexed (500 mg/m^2) with or without bevacizumab (7.5 mg/kg) every three weeks for four cycles. All patients achieved partial response or stable disease following the four cycles of induction chemotherapy, then underwent maintenance treatment until disease progression occurred.

All patient data were collected at the time of enrollment, including the chief complaint, disease history, physical examination, imaging examinations, and biochemical laboratory tests. Thoracoabdominal computed tomography scans were performed at baseline and every six weeks until disease progression. Tumor response was assessed by local investigators using Response Evaluation Criteria in Solid Tumors version 1.1. At progression, patients were followed up for further therapy and evaluation of survival.

Tumor assessment was performed prior to initiation (within 28 days before the first treatment as the baseline), once every two cycles, then at post-treatment follow-up visits until RECIST-defined progression. All examinations were performed in our Peking Union Medical College Hospital inpatient or outpatient units. The primary efficacy endpoint was progression-free survival (PFS), which was defined as the time from the first administration of maintenance therapy until disease progression or death. Tumor measurements were evaluated using Response Evaluation

Criteria in Solid Tumors (RECIST) (Version 1.1) to determine complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). Complete response and PR required confirmation ≥4 weeks after the initial response observation.

Safety and tolerability evaluations were performed during each cycle. Prior to induction of therapy, and during every cycle, a complete history was taken, a physical examination was performed, and physical scores were evaluated. A full blood cell count, urinalysis, serum biochemistry, coagulation screen, bleeding time, creatine kinase, lactate dehydrogenase, and electrocardiogram (ECG) were assessed.

Statistical analysis

Descriptive statistics were used to summarize patient baseline characteristics. Fisher's exact test for categorical data and the Mann-Whitney U test for continuous variables were used to assess between-group differences at baseline. Progression-free survival was defined as the time from the start of chemotherapy to the first documented disease progression or to the date of death. Patients who had not progressed or died at the time of analysis were censored at the date of the last follow-up. We estimated survival distributions (PFS) using the Kaplan-Meier method, and compared differences between groups using the log-rank test. Potential predictors for survival were evaluated using Cox regression. All statistical analyses were two-sided, and $P < 0.05$ was considered statistically significant. We included variables from the univariate analysis with $P < 0.1$ in the multivariate analysis. All statistical analyses were performed using SPSS 21.0 software.

The efficacy endpoint compared in this study was PFS, which was defined from registration until disease progression or death for any reason. Response was classified as CR, PR, SD, or PD according to RECIST 1.1. Adverse events were graded using Common Terminology Criteria for Adverse Events, version 4.0 (CTCAE 4.0), and were summarized by event type and worst recorded grade per patient across all therapy cycles administered. The median values of the time-to-event endpoints were calculated using the Kaplan-Meier method and 95% confidence intervals (CIs) were generated. *P*-values from comparisons of the odds ratio between the treatments were calculated using Fisher's exact test.

Results

Demographic data

Data from 35 patients diagnosed with advanced NS-NSCLC in our lung cancer center between April 2016 and September 2018 and who met the selection criteria were reviewed in this study (Pem-Pt/Pem, $N = 12$; Pem-Pt/Pem + Bev, $N = 11$; Pem-Pt + Bev/Pem + Bev, $N = 12$) (Table 1).

Patient baseline characteristics were similar for several parameters across the treatment cohorts including age, sex, disease stage, ECOG PS, and smoking status (Table 1). The study included 20 (57.1%) male and 15 (42.9%) female patients with a median age of 35 years ranging from 40 to 75 years. Most of the patients had an ECOG PS of 0 to 1 (Table 1).

Table 1 Baseline demographic data

	Subject (n [%])			Total
	Group A (Pem-Pt/Pem)	Group B (Pem-Pt/Pem + Bev)	Group C (Pem-Pt + Bev/Pem + Bev)	
No.	13 (37.1%)	9 (25.7%)	13 (37.1%)	35
Gender				
Men	9 (69.2%)	4 (44.4%)	7 (53.8%)	20 (57.1%)
Women	4 (30.8%)	5 (55.6%)	6 (46.2%)	15 (42.9%)
Age				
Median age	62	50	60	59
Range	48–71	40–73	44–75	40–75
ECOG PS score				
0	5 (38.5%)	4 (44.4%)	4 (30.8%)	13 (37.1%)
1	8 (61.5%)	5 (55.6%)	9 (69.2%)	17 (62.9%)
Histological type				
ADC	11 (84.6%)	9 (100%)	13 (100%)	33 (94.3%)
NOS	2 (7.7%)	0	0	2 (5.7%)
History of smoking				
Yes	3 (23.1%)	5 (55.6%)	4 (30.7%)	12 (34.3%)
No	10 (76.9%)	4 (44.4%)	9 (69.2%)	18 (65.7%)

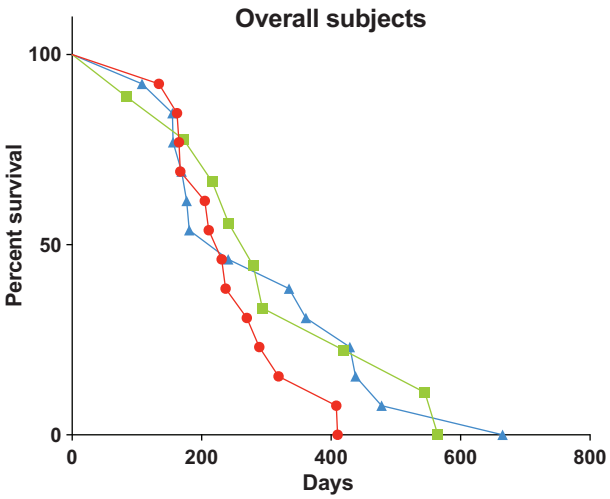

Figure 1 The median PFS among the three groups (—●—) Pem-Pt, (—■—) Pem-Pt/Pem+Pt, (—▲—) Pem-Pt+Bem/Pem+Bev.

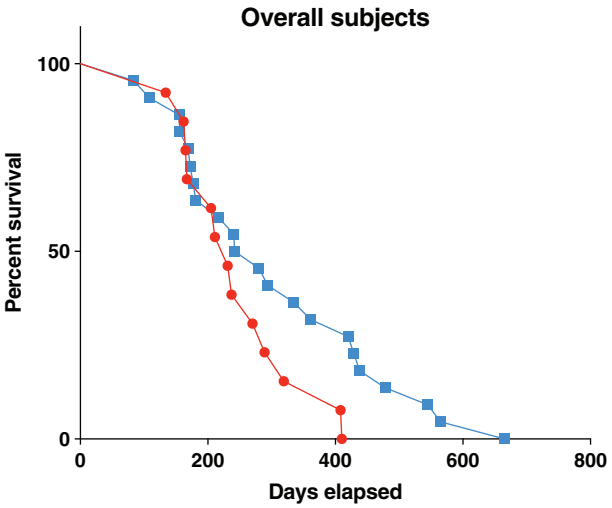

Figure 2 The median PFS for patients treated with or without bevacizumab (—●—) without Bev, (—■—) with Bev.

Effectiveness outcomes

The median PFS was slightly longer in the Pem-Pt/Pem + Bev group than that in the other groups, but this difference was not statistically significant (Pem-Pt/Pem + Bev 280 days; Pem-Pt/Pem 231 days; Pem-Pt + Bev/Pem + Bev 241 days; $P = 0.233$) (Fig 1). The median PFS was not significantly different between the group that received bevacizumab and the group that did not receive bevacizumab at any point during treatment (without Bevacizumab 242 days; with Bevacizumab 181 days; $P = 0.630$) (Fig 2).

In the subgroup of patients who received PR following four cycles of chemotherapy, the median PFS in the Pem-Pt/Pem + Bev group was 545 days compared with 231 days in the Pem-Pt/Pem group and 181 days in the Pem-Pt + Bev/Pem + Bev group (95% CI 156.050–383.950; $P = 0.244$) (Fig 3a). In the stable disease subgroup, the median PFS did not differ among the treatment groups (95% CI 198.273–257.727; $P = 0.407$). (Fig 3b).

Safety profile

No unexpected or grade ≥ III AEs occurred. Adverse events of grade I or II are summarized in Table 2.

Discussion

Clinically, patients have been unable to apply Avastin for various reasons, such as bleeding, impaired renal function, arterial thrombosis, hypertension crisis, poor wound healing, gastrointestinal tract perforation, and so on. There is little data to evaluate the optimal timing for adding bevacizumab when those contraindications are removed. We retrospectively analyzed this set of data and found that it was still effective to add bevacizumab in the maintenance-therapy period.

Pemetrexed[26] is a fourth-generation antimetabolic chemotherapeutic drug. Pemetrexed is a cytotoxic dihydrofolate reductase inhibitor that affects nucleic acid synthesis and inhibits three folate-dependent enzymes. A phase III study that compared pemetrexed/cisplatin and gemcitabine/cisplatin for the treatment of advanced NSCLC (JMDB study)[30] showed that pemetrexed/cisplatin was more effective for treatment of nonsquamous NSCLC, as evidenced by extended OS (11.8 months) and PFS (5.3 months). In our study, the median PFS in the Pem-Pt/Pem group was 7.7 months (231 days), which was longer than that observed in the JMDB study (5.3 months). This finding demonstrated that patients with advanced nonsquamous NSCLC benefited from pemetrexed as continued maintenance therapy, which was consistent with the results of the PARAMOUNT[21] and JMEN[22] studies.

Bevacizumab is an antiangiogenic drug that promotes tumor vascular degeneration, inhibits neovascularization, and normalizes vascular permeability. Bevacizumab combined with carboplatin/paclitaxel[8] extended OS of the nonsquamous NSCLC by more than one year, and the overall response rate of this population more than doubled. The OS of the lung adenocarcinoma subgroup was 14.2 months and the risk of mortality was reduced by 31%. Therefore, the NCCN guidelines (2011 V1.) recommended treatment with bevacizumab and chemotherapy or pemetrexed with cisplatin as the standard first-line treatment options for patients with negative or unknown EGFR mutations. In our study, the PFS in Pem-Pt /Pem + Bev was 6.03 months, (181 days), which was similar to the results of the

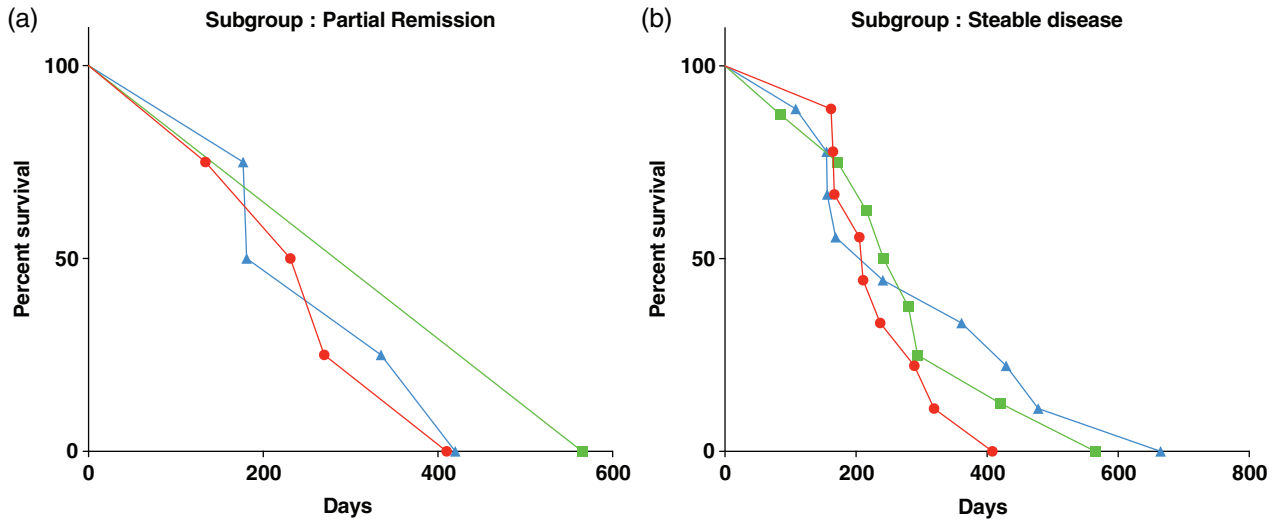

Figure 3 (**a**) The median PFS of patients who achieved PR among the three groups (—●—) Pem-Pt/Pem, (—■—) Pem-Pt/Pem+Bev, (—▲—) Pem-Pt+Bev/Pem+Bev. (**b**) The median PFS of patients who achieved SD among the three groups (—●—) Pem-Pt/Pem, (—■—) Pem-Pt/Pem+Bev, (—▲—) Pem-Pt +Bev/Pem+Bev.

Table 2 Grade I or II adverse events with pemetrexed-platinum chemotherapy with or without bevacizumab in patients with advanced NSCLC

Adverse events††	Pem-Pt/Pem	Pem-Pt/Pem + Bev	Pem-Pt + Bev/Pem + Bev
Vomiting	5 (38.5%)	2 (22.2%)	3 (23.1%)
Myelosuppression	4 (30.8%)	2 (22.2%)	4 (30.8%)
Hypertension	0	1 (11.1%)	3 (23.1%)
Epistaxis	0	1 (11.1%)	1 (7.7%)
Proteinuria	0	0	1 (7.7%)

†None of the patients experienced grade III or IV adverse events.

ECOG4599[8] (6.2 months) study, a key study that contributed to the first-line indication for bevacizumab.

The AVAPERL[15] study further confirmed that bevacizumab and pemetrexed were a "strong combination." Maintenance with bevacizumab and pemetrexed or with bevacizumab alone resulted in PFS of 8.6 months and 3.9 months, respectively (hazard ratio 0.42; 95% confidence interval 0.28–0.64; $P < 0.001$). The PFS durations of patients with stable disease were 6.8 months and 3.3 months for those treated with both drugs and those treated with bevacizumab only, respectively (risk ratio 0.63, 95% confidence interval 0.41 to 0.97; $P = 0.036$). The PFS from the induction of chemotherapy was also significantly longer in the two-drug maintenance group than in the monotherapy maintenance group (10.2 months vs. 6.6 months; risk ratio 0.50, 95% confidence interval 0.40–0.72; $P < 0.001$). The PointBreak[13] study, which was similar to the AVAPERL study, showed that maintenance therapy with bevacizumab plus pemetrexed following induction with bevacizumab plus platinum/pemetrexed resulted in longer survival. A meta-analysis[27] showed that pemetrexed plus bevacizumab as continued maintenance therapy prolonged PFS. The results of our study showed that inclusion of bevacizumab with first-line platinum-based chemotherapy or maintenance therapy improved survival in patients with advanced non-squamous NSCLC who had achieved PR or SD during induction chemotherapy. These data contradicted the results of previous studies, and showed that combination therapy with pemetrexed and bevacizumab as a maintenance strategy did not improve management of advanced NSCLC. In our study, the median PFS in the Pem-Pt/Pem group was 7.7 months (231 days), which was longer than that observed in the PARAMOUNT[21] (4.1 months). The median PFS in the Pem-Pt + Bev/Pem + Bev group (8.0 months, 241 days) was longer than that observed in the AVAPER[15] study (7.4 months). These differences may have been due to our inclusion criterion of patients who had achieved PR or SD after induction chemotherapy. In this context, treatment with bevacizumab may have increased the number of patients who achieved PR or SD during induction chemotherapy. For those patients who achieved PR or SD following induction chemotherapy without bevacizumab, addition of bevacizumab as maintenance therapy did not result in additional improvement in outcomes. However, addition of bevacizumab early in the treatment regimen may increase the rate of disease control and confer survival benefits.

This was a retrospective study with no accepted fact that addition of bevacizumab can improve PFS of non-squamous NSCLC. However, our study showed that addition of bevacizumab to induction chemotherapy may have increased the disease control rate. Previous studies[2, 7, 12–14, 16, 18, 23, 27–31] showed that addition of bevacizumab increased disease control rate, which indicated that bevacizumab should be administered as early as possible in the therapy regimen. Tumor neovascularization often continues to progress in NSCLC, and maintenance therapy can inhibit tumor neovascularization. If clinical benefits and safety criteria are met, patients are advised to maintain treatment.

This study had several limitations. First, this was a retrospective, nonrandomized study that was conducted at a single institution. Therefore, it is possible that unintentional selection bias may have occurred. Second, the number of patients included was small. Although our study showed that treatment with pemetrexed plus bevacizumab was associated with improved OS, this was a secondary endpoint of the study, and the sample size was not large enough to determine any other significant associations. Third, no biomarker analysis was performed. For example, the distribution of *EGFR* mutation status in the enrolled patients, and the effect of the mutation status on the results was not evaluated. Future prospective studies with larger cohorts are needed to further evaluate the findings of this study.

In conclusion, studies have shown that patients who benefit from first-line treatment also show increased survival with increased duration of antivascular maintenance therapy. Although our study result is negative, we also recommend that early induction of treatment results in better outcomes.

Disclosure

The authors made no disclosures.

References

1 Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin* 2018; **68**: 7–30.

2 Li X, Abbas M, Li Y *et al.* Comparative effectiveness of pemetrexed-platinum doublet chemotherapy with or without bevacizumab as first-line therapy for treatment-naive patients with advanced nonsquamous non-small-cell lung cancer in China. *Clin Ther* 2019; **41**: 518–29.

3 Gubens MA, Davies M. NCCN guidelines updates: New immunotherapy strategies for improving outcomes in non-small cell lung cancer. *J Natl Compr Canc Netw* 2019; **17**: 574–8.

4 Park JO, Kim SW, Ahn JS *et al.* Phase III trial of two versus four additional cycles in patients who are nonprogressive after two cycles of platinum-based chemotherapy in non small-cell lung cancer. *J Clin Oncol* 2007; **25**: 5233–9.

5 Hotta K, Matsuo K, Ueoka H, Kiura K, Tabata M, Tanimoto M. Meta-analysis of randomized clinical trials comparing cisplatin to carboplatin in patients with advanced non-small-cell lung cancer. *J Clin Oncol* 2004; **22**: 3852–9.

6 Schiller JH, Harrington D, Belani CP *et al.* Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N Engl J Med* 2002; **346**: 92–8.

7 Zhou C, Wu YL, Chen G *et al.* BEYOND: A randomized, double-blind, placebo-controlled, multicenter, phase III study of first-line carboplatin/paclitaxel plus bevacizumab or placebo in Chinese patients with advanced or recurrent nonsquamous non-small-cell lung cancer. *J Clin Oncol* 2015; **33**: 2197–204.

8 Sandler A, Gray R, Perry MC *et al.* Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med* 2006; **355**: 2542–50.

9 Niho S, Kunitoh H, Nokihara H *et al.* Randomized phase II study of first-line carboplatin-paclitaxel with or without bevacizumab in Japanese patients with advanced non-squamous non-small-cell lung cancer. *Lung Cancer* 2012; **76**: 362–7.

10 Johnson DH, Fehrenbacher L, Novotny WF *et al.* Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. *J Clin Oncol* 2004; **22**: 2184–91.

11 Sandler AB, Schiller JH, Gray R *et al.* Retrospective evaluation of the clinical and radiographic risk factors associated with severe pulmonary hemorrhage in first-line advanced, unresectable non-small-cell lung cancer treated with carboplatin and paclitaxel plus bevacizumab. *J Clin Oncol* 2009; **27**: 1405–12.

12 Reck M, von Pawel J, Zatloukal P *et al.* Overall survival with cisplatin-gemcitabine and bevacizumab or placebo as first-line therapy for nonsquamous non-small-cell lung cancer: Results from a randomised phase III trial (AVAiL). *Ann Oncol* 2010; **21**: 1804–9.

13 Patel JD, Socinski MA, Garon EB *et al.* 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* 2013; **31**: 4349–57.

14 Saito H, Fukuhara T, Furuya N *et al.* Erlotinib plus bevacizumab versus erlotinib alone in patients with EGFR-positive advanced non-squamous non-small-cell lung cancer (NEJ026): Interim analysis of an open-label, randomised, multicentre, phase 3 trial. *Lancet Oncol* 2019; **20**: 625–35.

15 Barlesi F, Scherpereel A, Rittmeyer A *et al.* 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* 2013; **31**: 3004–11.
16 Crino L, Dansin E, Garrido P *et al*. Safety and efficacy of first-line bevacizumab-based therapy in advanced non-squamous non-small-cell lung cancer (SAiL, MO19390): A phase 4 study. *Lancet Oncol* 2010; **11**: 733–40.
17 Gerber DE, Schiller JH. Maintenance chemotherapy for advanced non-small-cell lung cancer: New life for an old idea. *J Clin Oncol* 2013; **31**: 1009–20.
18 Lynch TJ Jr, Spigel DR, Brahmer J *et al*. Safety and effectiveness of bevacizumab-containing treatment for non-small-cell lung cancer: Final results of the ARIES observational cohort study. *J Thorac Oncol* 2014; **9**: 1332–9.
19 Barlesi F, Mazieres J, Merlio JP *et al*. Routine molecular profiling of patients with advanced non-small-cell lung cancer: Results of a 1-year nationwide programme of the French cooperative thoracic intergroup (IFCT). *Lancet* 2016; **387**: 1415–26.
20 Karayama M, Inui N, Fujisawa T *et al*. Maintenance therapy with pemetrexed and bevacizumab versus pemetrexed monotherapy after induction therapy with carboplatin, pemetrexed, and bevacizumab in patients with advanced non-squamous non small cell lung cancer. *Eur J Cancer* 2016; **58**: 30–7.
21 Paz-Ares L, de Marinis F, Dediu M *et al*. 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* 2012; **13**: 247–55.
22 Ciuleanu T, Brodowicz T, Zielinski C *et al*. 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* 2009; **374**: 1432–40.
23 Barlesi F, Scherpereel A, Gorbunova V *et al*. Maintenance bevacizumab-pemetrexed after first-line cisplatin-pemetrexed-bevacizumab for advanced nonsquamous nonsmall-cell lung cancer: Updated survival analysis of the AVAPERL (MO22089) randomized phase III trial. *Ann Oncol* 2014; **25**: 1044–52.
24 Ettinger DS, Aisner DL, Wood DE *et al*. NCCN guidelines insights: Non-small cell lung cancer, version 5.2018. *J Natl Compr Canc Netw* 2018; **16**: 807–21.
25 Reck M, Popat S, Reinmuth N *et al*. Metastatic non-small-cell lung cancer (NSCLC): ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2014; **25** (Suppl 3): iii27–39.
26 Shih C, Chen VJ, Gossett LS *et al*. LY231514, a pyrrolo [2,3-d]pyrimidine-based antifolate that inhibits multiple folate-requiring enzymes. *Cancer Res* 1997; **57**: 1116–23.
27 Shan F, Zhang B, Sun L, Xie L, Shen M, Ruan S. The role of combination maintenance with pemetrexed and bevacizumab for advanced stage nonsquamous non-small cell lung cancer: A systematic review and meta-analysis. *Biomed Res Int* 2018; **2018**: 5839081.
28 Reck M, von Pawel J, Zatloukal P *et al*. Phase III trial of cisplatin plus gemcitabine with either placebo or bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer: AVAil. *J Clin Oncol* 2009; **27**: 1227–34.
29 Dansin E, Cinieri S, Garrido P *et al*. MO19390 (SAiL): Bleeding events in a phase IV study of first-line bevacizumab with chemotherapy in patients with advanced non-squamous NSCLC. *Lung Cancer* 2012; **76**: 373–9.
30 Wu YL, Lu S, Cheng Y *et al*. Efficacy and safety of pemetrexed/cisplatin versus gemcitabine/cisplatin as first-line treatment in Chinese patients with advanced nonsquamous non-small cell lung cancer. *Lung Cancer* 2014; **85**: 401–7.
31 Hakozaki T, Okuma Y, Hashimoto K, Hosomi Y. Correlation between the qualification for bevacizumab use and the survival of patients with non-small cell lung cancer harboring the epidermal growth factor receptor mutation: A retrospective analysis. *J Cancer Res Clin Oncol* 2019; **145**: 2555–64.

