

## 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)

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### ABSTRACT

#### Purpose

Maintenance therapy is associated with improved survival in patients with non–small-cell lung cancer (NSCLC), but few studies have compared active agents in this setting. AVAPERL evaluated the safety and efficacy of bevacizumab with or without pemetrexed as continuation maintenance treatment.

#### Patients and Methods

Patients with advanced nonsquamous NSCLC received first-line bevacizumab 7.5 mg/kg, cisplatin 75 mg/m<sup>2</sup>, and pemetrexed 500 mg/m<sup>2</sup> once every 3 weeks for four cycles. Those achieving response or stable disease were randomly assigned at a ratio of 1:1 to maintenance bevacizumab 7.5 mg/kg or bevacizumab 7.5 mg/kg plus pemetrexed 500 mg/m<sup>2</sup> once every 3 weeks until disease progression or unacceptable toxicity. The primary end point was progression-free survival (PFS) after random assignment.

#### Results

In total, 376 patients received induction treatment, 71.9% achieved disease control, and 67.3% were randomly assigned to maintenance therapy, with 125 and 128 receiving single-agent bevacizumab and bevacizumab plus pemetrexed treatment, respectively. At a median follow-up of 8.1 months, PFS from random assignment was significantly improved in the bevacizumab plus pemetrexed arm (median, 3.7 v 7.4 months; hazard ratio, 0.48; 95% CI, 0.35 to 0.66; *P* < .001) per a stratified model. The PFS benefit extended across age, performance status, smoking history, and induction response (stable disease v partial response) subgroups. Any grade, grade ≥ 3, and serious adverse events occurred more often with bevacizumab plus pemetrexed maintenance. No new safety signals were observed.

#### Conclusion

In an unselected population of patients with nonsquamous NSCLC who had achieved disease control with platinum-based chemotherapy plus bevacizumab, bevacizumab plus pemetrexed maintenance was associated with a significant PFS benefit compared with bevacizumab alone. The combination was well tolerated.

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### INTRODUCTION

For patients with advanced or metastatic non–small-cell lung cancer (NSCLC), prognosis is poor, and 1-year survival rates are 30% to 40%.<sup>1</sup> Therapy is palliative, and tumor response rates are between 25% and 35%.<sup>1</sup> First-line cytotoxic combinations reached an apparent efficacy plateau more than a

decade ago.<sup>2,3</sup> Antiangiogenic therapy, which targets tumor vasculature rather than cancer cells,<sup>4</sup> was anticipated to prolong survival in NSCLC. The phase III ECOG (Eastern Cooperative Oncology Group) 4599 study established bevacizumab, a monoclonal antibody against vascular endothelial growth factor A, with carboplatin plus paclitaxel induction followed by bevacizumab continuation maintenance

as a standard first-line treatment for patients with advanced nonsquamous NSCLC. Patients treated with bevacizumab 15 mg/kg once every 3 weeks experienced significant improvement in progression-free (PFS; median, 6.2 v 4.5 months; hazard ratio [HR], 0.66;  $P < .001$ ) and overall survival (OS; median, 12.3 v 10.3 months; HR, 0.79;  $P = .003$ ) compared with those treated with induction carboplatin plus paclitaxel alone.<sup>5</sup> The AVAIL (Avastin in Lung) study confirmed the PFS benefit of adding bevacizumab to first-line cisplatin/gemcitabine (bevacizumab 7.5 mg/kg once every 3 weeks: median PFS, 6.7 v 6.1 months; HR, 0.75; 95% CI, 0.62 to 0.91;  $P = .003$ ; bevacizumab 15 mg/kg once every 3 weeks: median PFS, 6.5 v 6.1 months; HR, 0.82; 95% CI, 0.68 to 0.98;  $P = .03$ ),<sup>6</sup> although OS was not significantly improved (bevacizumab 7.5 mg/kg once every 3 weeks: median OS, 13.6 v 13.1 months; HR, 0.93;  $P = .42$ ; bevacizumab 15 mg/kg once every 3 weeks: median OS, 13.4 v 13.1 months; HR, 1.03;  $P = .76$ ).<sup>7</sup>

Pemetrexed, an antineoplastic agent that disrupts folate-dependent metabolism,<sup>8</sup> has also been safely and effectively incorporated into first-line platinum-doublet regimens in nonsquamous NSCLC.<sup>9</sup> In a phase III study, maintenance pemetrexed administered for the first time after four cycles of platinum-based chemotherapy was shown to improve median PFS (4.3 v 2.6 months; HR, 0.50;  $P < .001$ ) and median OS (13.4 v 10.6 months; HR, 0.79;  $P = .012$ ) compared with placebo in stage IIIB/IV NSCLC.<sup>10</sup> In the phase III PARAMOUNT study, maintenance pemetrexed administered after pemetrexed plus cisplatin induction significantly reduced the risk of disease progression (PD) compared with placebo (HR, 0.62; 95% CI, 0.49 to 0.79;  $P < .001$ ).<sup>11</sup>

To date, few phase III trials have reported comparative data on maintenance phase agents and combinations.<sup>12</sup> Phase II studies have explored the combination of bevacizumab, pemetrexed, and a platinum for induction therapy when followed by continuation maintenance therapy with one or both agents.<sup>13,14</sup> These have reported encouraging median PFS (approximately 7.8 months) and OS ( $\geq 14.1$  months) rates in first-line nonsquamous NSCLC, with acceptable toxicity. AVAPERL, which compared continuation maintenance with bevacizumab monotherapy and bevacizumab plus pemetrexed, was a randomized phase III trial designed to elucidate efficacy and safety outcomes associated with a combination maintenance strategy.

## PATIENTS AND METHODS

The protocol was approved by institutional review boards and health authorities at participating centers. The study followed the Declaration of Helsinki and Good Clinical Practice guidelines.<sup>15</sup>

### Eligibility

Eligible patients were age  $\geq 18$  years with previously untreated, histologically or cytologically documented inoperable locally advanced (stage IIIB disease with supraclavicular lymph node or malignant pleural or pericardial effusion),<sup>16</sup> metastatic or recurrent nonsquamous NSCLC. Informed consent,  $\geq$  one unidimensionally measurable lesion meeting RECIST version 1.1, ECOG performance status (PS) at induction of 0 to 2, and adequate hematologic, liver, and renal (including creatinine clearance  $\geq 50$  mL/min at baseline and  $\geq 45$  mL/min before the start of any subsequent cycle) functions were required. Asymptomatic brain metastases were allowed.<sup>17</sup> Key exclusion criteria included predominantly squamous histology, history of grade  $\geq 2$  hemoptysis, and uncontrolled hypertension.

### Study Design and Treatment

AVAPERL was a randomized, open-label, multicenter phase III trial. In the induction phase (Fig 1), patients received bevacizumab 7.5 mg/kg intravenously (IV; dose previously used in AVAIL<sup>6</sup>), cisplatin 75 mg/m<sup>2</sup> IV, and pemetrexed 500 mg/m<sup>2</sup> on day 1 of each of four 21-day cycles. Pemetrexed was administered over 10 minutes. Cisplatin was administered over 2 hours. Bevacizumab was initially administered over 90 minutes; if well tolerated, subsequent infusions were administered over 60 and, eventually, 30 minutes. Patients achieving complete response (CR), partial response (PR), or stable disease (SD) after induction were eligible for the maintenance phase, in which they were randomly assigned at a ratio of 1:1 to bevacizumab 7.5 mg/kg IV or bevacizumab 7.5 mg/kg IV plus pemetrexed 500 mg/m<sup>2</sup> IV once every 3 weeks.

Throughout the study, pemetrexed-treated patients received standard supplementation with folic acid orally (350 to 1000  $\mu$ g daily), vitamin B<sub>12</sub> intramuscularly (1,000  $\mu$ g once every three cycles), and dexamethasone prophylaxis orally (4 mg twice per day) on days -1, 1, and 2 of each cycle. Patients were stratified by sex, smoking status, and tumor response (SD v PR) at random assignment. Maintenance treatment was continued until PD, death, or withdrawal of consent.

### Dose Modifications and Delays

Bevacizumab dose modifications were not allowed, but treatment could be delayed or omitted for one to two consecutive cycles. If on-study weight change  $> 10\%$  occurred, the bevacizumab dose was recalculated. In cases of hematologic toxicity, treatment with cisplatin and pemetrexed could be delayed up to 3 weeks until the absolute neutrophil count at day 1 was  $\geq 1.5 \times 10^9/L$  and platelet count was  $> 100 \times 10^9/L$ . The doses of pemetrexed and cisplatin could then be reduced. For grade  $\geq 3$  nonhematologic toxicities (except for alopecia and neurotoxicity), pemetrexed and cisplatin were withheld until resolution to grade 1, and thereafter, doses were reduced. For grade 2 neurotoxicity, the cisplatin dose was reduced by 50%; grade 3 or 4 neurotoxicity warranted permanent cisplatin discontinuation.

### Assessments

During induction, tumor response was assessed at baseline and at the end of cycles two and four. During maintenance, tumors were assessed at the end of cycle two and every three cycles thereafter. All assessments were performed by investigators using RECIST version 1.1. Adverse event (AE) information was collected at each cycle and at every 3-month follow-up. These were assessed using the National Cancer Institute Common Terminology Criteria version 3.0. AEs were coded using the Medical Dictionary for Regulatory Activities.

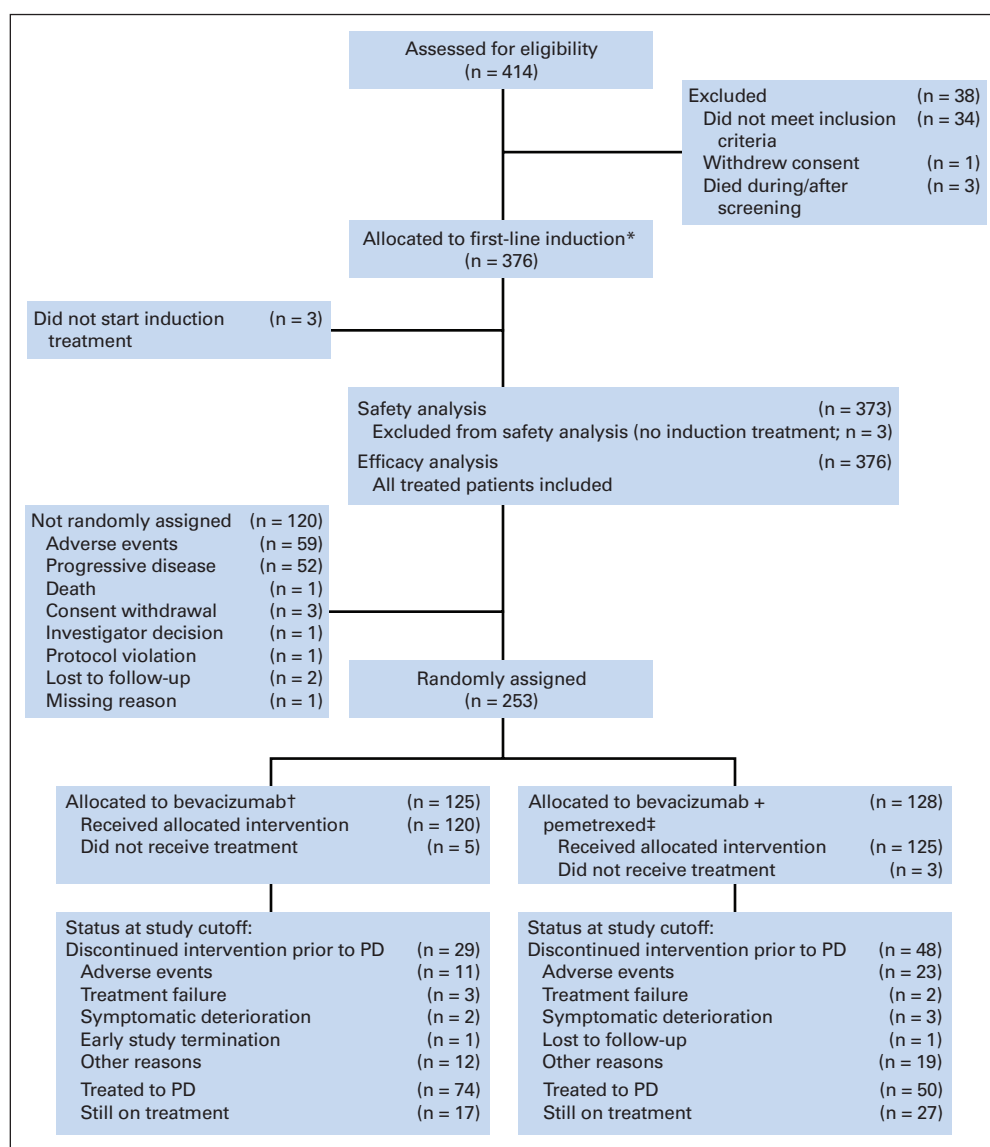
### Statistical Methods

The efficacy population included patients allocated to maintenance treatment regardless of whether they received it. The safety population included patients who received at least one dose of any study treatment.

The primary end point was PFS, which was defined as the interval from the date of random assignment until either first PD or death resulting from any cause, whichever occurred earlier. All patients received a scheduled tumor assessment per protocol before random assignment, and only those with SD, PR, or CR were eligible for random assignment. However, a complete rebaseline tumor assessment was not performed before random assignment.

Kaplan-Meier estimates were employed. The analysis of PFS from random assignment was stratified by sex, smoking status, and induction response. A stratified Cox regression model was used to calculate HRs. Patients without a PFS event were censored at the date of the last available tumor assessment at which they were known to be without PD. Patients without post-random assignment tumor assessment were censored at the date of random assignment.

Secondary end points were OS, defined as the time from random assignment to death resulting from any cause; best overall response rate (ORR), defined as the best (confirmed) response from induction period; duration of response, defined as the interval from first documented CR/PR until PD or death resulting from any cause; duration of disease control, defined as the interval from first documented CR/PR or SD until PD or death resulting from any cause; and quality of life. Tumor assessment performed before induction



**Fig 1.** AVAPERL CONSORT diagram and treatment schema. PD, progressive disease. (\*) Bevacizumab 7.5 mg/kg plus cisplatin 75 mg/m<sup>2</sup> plus pemetrexed 500 mg/m<sup>2</sup> once every 3 weeks for four cycles. (†) Bevacizumab 7.5 mg/kg once every 3 weeks until PD, unacceptable toxicity, or withdrawal of consent. (‡) Bevacizumab 7.5 mg/kg plus pemetrexed 500 mg/m<sup>2</sup> once every 3 weeks until PD, unacceptable toxicity, or withdrawal of consent.

phase was used as comparator/baseline. Differences in response, 95% Hauck-Anderson CIs, and a two-sided Cochran-Mantel-Haenszel  $\chi^2$  test stratified by randomization variables are presented for best ORR.

The study power was based on PFS defined from the time of random assignment. On that basis, 228 patients randomly assigned to maintenance therapy would experience 210 events, assuming median PFS values of 15 and 24 weeks in the bevacizumab alone and bevacizumab plus pemetrexed arms, respectively (HR, 0.68), with 80% power and a two-sided  $\alpha$  level of 5%. Assuming that 10% of patients would withdraw during induction and that the postinduction disease control rate would be 70%, 362 patients would need to be enrolled in induction. The study was not powered to detect statistical differences in OS. There was no interim efficacy analysis. Regular safety reviews of data were performed by an independent data safety monitoring board.

## RESULTS

### Patient Disposition

Between August 2009 and July 2010, 414 patients were screened at 82 centers in 11 countries. Among the 376 patients enrolled, 123

were not randomly assigned to maintenance treatment (Fig 1). One patient without measurable disease at induction baseline was not included in the best ORR analysis. Induction-phase disease control was confirmed in 71.9% of patients (269 of 374) with measurable disease at baseline, with 85 patients (22.7%) achieving PR and 184 (49.2%) achieving SD. There were no CRs. Sixty-seven percent (253 of 376) of patients receiving induction treatment were randomly assigned to receive maintenance therapy: 125 patients to maintenance bevacizumab and 128 to maintenance bevacizumab plus pemetrexed. Five patients randomly assigned to the former and three to the latter arm did not subsequently receive any study treatment. Patient and disease characteristics were comparable between maintenance arms (Table 1).

### Treatment

The median time from the end of induction to random assignment was 3 weeks, with no imbalance between arms. A total of 282 patients, including all patients randomly assigned to maintenance,

**Table 1.** Baseline Patient Demographics and Clinical Characteristics

Characteristic	Safety Population (n = 373)		Maintenance Treatment			
			Bevacizumab (n = 120)		Bevacizumab Plus Pemetrexed (n = 125)	
	No.	%	No.	%	No.	%
Age < 65 years	257	68.9*	85	70†	88	70.4‡
Sex						
Male	220	59.0	68	56.7	72	57.6
Female	153	41.0	52	43.3	53	42.4
ECOG PS§						
At induction						
0	166	45.6	50	42.7	65	52.4
1	192	52.7	65	55.6	57	46.0
2	6	1.6	2	1.7	2	1.6
At randomization						
0	73	32.9	33	31.7	35	33.7
1	141	63.5	65	62.5	67	64.4
2	8	3.6	6	5.8	2	1.9
Current disease stage						
IIIB	28	7.5	13	10.8	7	5.6
IV	345	92.5	107	89.2	118	94.4
Histology						
Adenocarcinoma	329	88.2	110	91.7	107	85.6
Large-cell carcinoma	34	9.1	9	7.5	12	9.6
Other	10	2.7	1	0.8	6	4.8
Smoking status§						
Current	104	28.0	30	25.2	28	22.2
Past	193	52.0	58	48.7	66	52.8
Never	74	19.9	31	26.1	31	24.8
Centrally located lung tumor¶	144	38.6	43	35.8	46	36.8
Cavitated tumor¶	17	4.6	7	5.8	6	4.8

Abbreviations: ECOG, Eastern Cooperative Oncology Group; PS, performance status.

\*Median age, 60 years (range, 27 to 83 years).

†Median age, 60 years (range, 41 to 75 years).

‡Median age, 60 years (range, 34 to 76 years).

§Some patients had missing data.

||Includes bronchioloalveolar carcinoma, mixed-cell type (> 50% nonsquamous), and other.

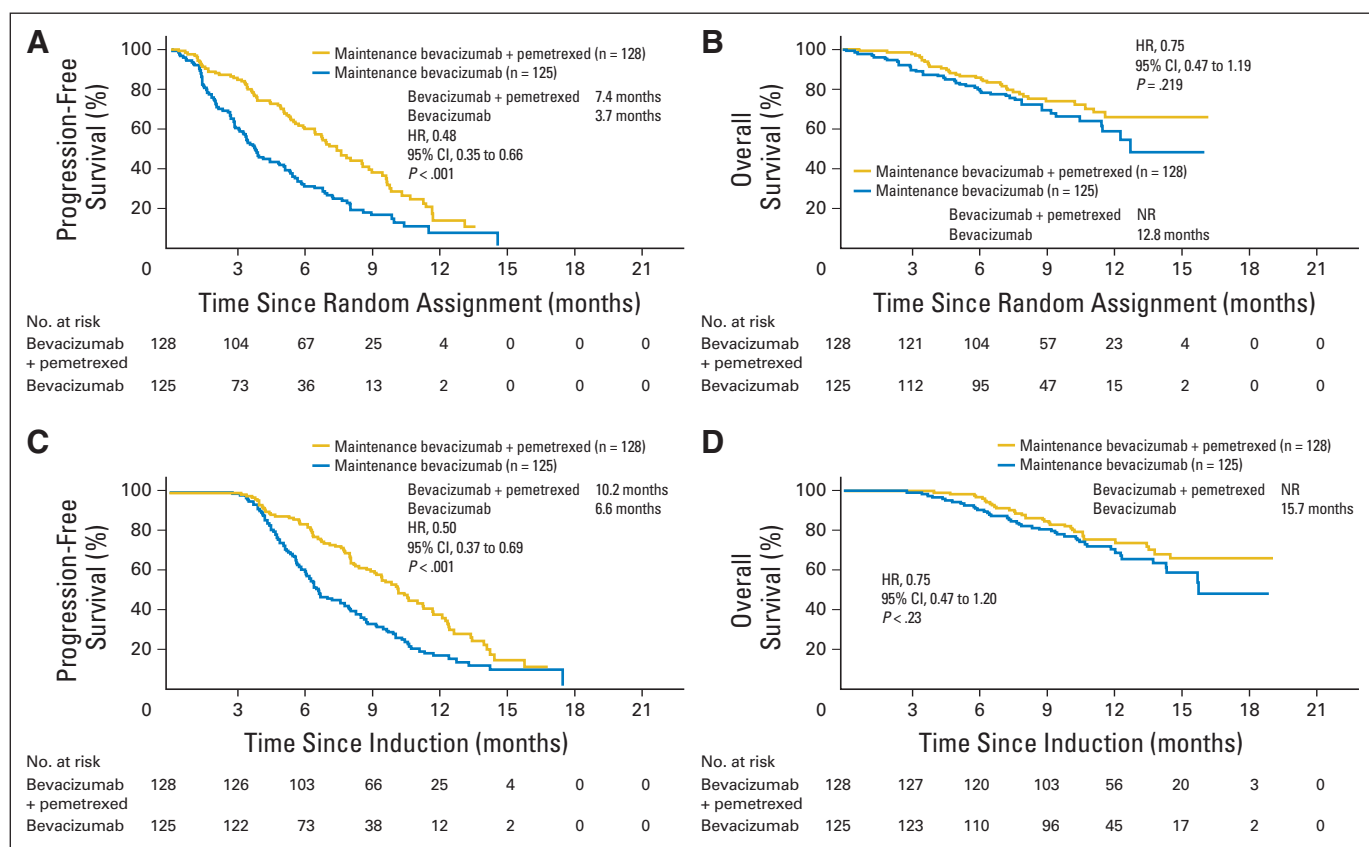
¶As defined by Sandler et al.<sup>18</sup>

received four cycles of induction cisplatin. Measured from the start of induction, patients randomly assigned to bevacizumab maintenance received a median of nine cycles (range, five to 27 cycles) of bevacizumab; those in the bevacizumab plus pemetrexed arm received a median of 11 cycles of both agents (bevacizumab: range, one to 24 cycles; pemetrexed: range, five to 24 cycles). During maintenance, 29 patients (24.2%) discontinued bevacizumab in the bevacizumab arm (11 because of an AE), and 47 (37.6%) discontinued bevacizumab in the bevacizumab plus pemetrexed arm (22 because of an AE); 46 patients (36.8%) in the latter arm prematurely discontinued pemetrexed (21 because of an AE). At clinical cutoff, 17 and 27 patients in the bevacizumab alone and bevacizumab plus pemetrexed arms, respectively, were still receiving bevacizumab. No imbalance resulting from subsequent therapies was observed between arms. Sixty-eight (57%) and 48 patients (39%) in the bevacizumab alone and bevacizumab plus pemetrexed arms, respectively, received subsequent post-PD treatment; the most common classes of subsequent therapeutic agents were tyrosine kinase inhibitors (33% and 26%, respectively) and taxanes (28% and 12%, respectively).

## Efficacy

The median follow-up time after random assignment was 8.1 months (range, 0 to 16.2 months). PFS events for the efficacy analysis occurred in 104 (83.2%) and 81 patients (63.3%) in the bevacizumab alone and bevacizumab plus pemetrexed arms, respectively. Seventeen patients in the bevacizumab alone arm and 11 patients in the bevacizumab plus pemetrexed arm without post-random assignment baseline tumor assessment were censored at the date of random assignment. The median PFS times from random assignment were 3.7 and 7.4 months for the bevacizumab alone and bevacizumab plus pemetrexed arms (HR, 0.48; 95% CI, 0.35 to 0.66;  $P < .001$ ), respectively (Fig 2). An analysis of PFS from first induction treatment was consistent with results as measured from random assignment, with medians of 6.6 months (95% CI, 6.0 to 7.8 months) in the bevacizumab arm and 10.2 months (95% CI, 9.1 to 11.7 months) in the bevacizumab plus pemetrexed arm, with HRs for progression of 0.50 (95% CI, 0.37 to 0.69;  $P < .001$ ) using the stratified model and 0.54 (95% CI, 0.40 to 0.72) using an unstratified model.

The PFS benefit of bevacizumab plus pemetrexed (Fig 3) was evident in patients who had achieved PR after induction (3.9 v 8.6

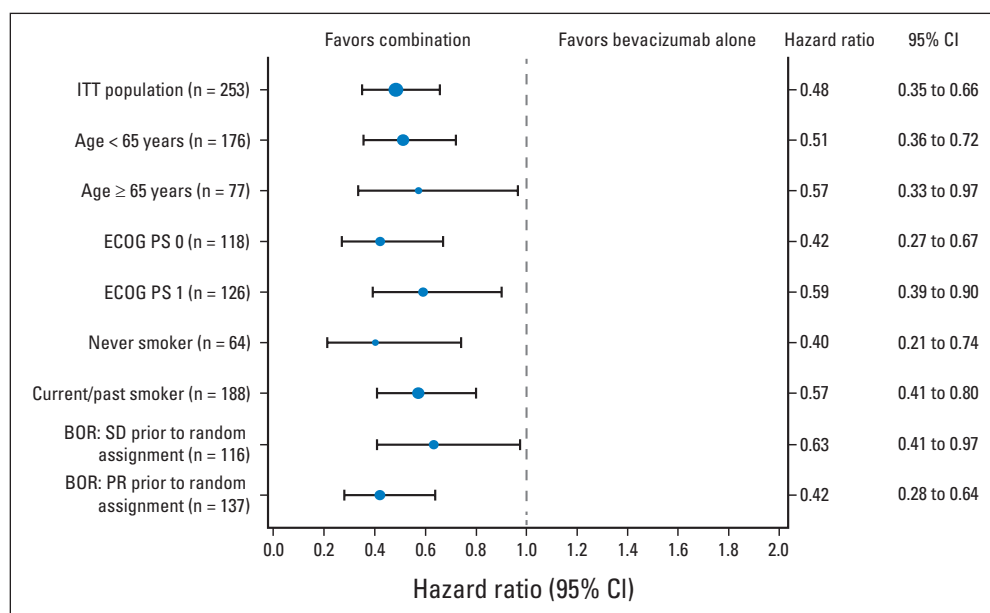


**Fig 2.** Kaplan-Meier estimates of the probability of (A) progression-free survival (PFS) and (B) overall survival (OS), as measured from randomization, and (C) PFS and (D) OS, as measured from first induction treatment, for patients randomly assigned to the maintenance arms in AVAPERL. HR, hazard ratio; NR, not reached.

months; HR, 0.42; 95% CI, 0.28 to 0.64;  $P < .001$ ) and in those with SD as best induction response (3.3 v 6.8 months; HR, 0.63; 95% CI, 0.41 to 0.97;  $P = .036$ ). Similarly, subgroup analysis of PFS from random assignment indicated that maintenance with bevacizumab plus pemetrexed was favored over bevacizumab alone irrespective of

patient age ( $< 65$  v  $\geq 65$  years), ECOG PS (0 v 1), and smoking history (never v current/past).

OS events occurred in 42 (33.6%) and 34 patients (26.6%) in the bevacizumab alone and bevacizumab plus pemetrexed arms, respectively. The comparison of survival experiences of the two arms is



**Fig 3.** Subgroup analysis of progression-free survival from random assignment benefit in AVAPERL. Hazard ratios are stratified for intent-to-treat (ITT) population but unstratified for subgroups. BOR, best overall response; ECOG, Eastern Cooperative Oncology Group; PR, partial response; PS, performance status; SD, stable disease.

shown in Figure 2B (HR, 0.75; 95% CI, 0.47 to 1.19;  $P = .219$ ). The median OS from the time of random assignment was 12.8 months (range, 0 to 16 months) in the bevacizumab arm and was not yet reached (range, 0.1 to 16.2 months) in the bevacizumab plus pemetrexed arm. After a median of 10.9 months of follow-up, the median OS from time of first induction was 15.7 months in the bevacizumab alone arm (range, 2.8 to 18.8 months) and was not yet reached in the bevacizumab plus pemetrexed arm (range, 3.0 to 19 months).

The best ORRs (all PRs) during the induction and maintenance period were 50.0% (95% CI, 40.9% to 59.1%) and 55.5% (95% CI, 46.4% to 64.3%) in the bevacizumab alone and bevacizumab plus pemetrexed arms, respectively, based on all-response assessments during the study. The treatment difference in best ORR was 5.5% (95% CI, -7.3% to 18.2%;  $P = .878$ ). The median duration of response was 9.2 months (range, 6.8 to 10.4 months) in the bevacizumab plus pemetrexed arm compared with 5.7 months (range, 4.9 to 7.2 months) in the bevacizumab alone arm (HR, 0.53; 95% CI, 0.34 to 0.84;  $P = .006$ ). The median duration of disease control was 4.9 months (range, 0 to 15.1 months) in the bevacizumab alone arm and 7.8 months (range, 0.5 to 15.1 months) in the bevacizumab plus pemetrexed arm (HR, 0.52; 95% CI, 0.38 to 0.70;  $P < .001$ ). A preliminary report on health-related quality of life found no significant

differences between patients in the maintenance arms<sup>19</sup>; full results will be published elsewhere.

### Safety

During maintenance, most AEs were grade 1 or 2, whereas 26 (21.7%) and 47 patients (37.6%) in the bevacizumab alone and bevacizumab plus pemetrexed arms, respectively, experienced a grade  $\geq 3$  AE. Most toxicities were nonhematologic. The most common any-grade AEs during the maintenance phase were nausea, hypertension, and asthenia (Table 2). During maintenance, incidence rates of any-grade hemoptysis were 1.7% and 2.4% in the bevacizumab alone and bevacizumab plus pemetrexed arms, respectively.

Throughout the study, patients in the bevacizumab plus pemetrexed arm experienced a higher incidence of grade  $\geq 3$  AEs and serious AEs than patients in the bevacizumab alone arm. The most common grade  $\geq 3$  AEs with onset during maintenance were hypertension and dyspnea (2.5% each) in the bevacizumab alone arm and neutropenia (5.6%), hypertension (4.8%), and anemia (3.2%) in the bevacizumab plus pemetrexed arm. During maintenance, grade  $\geq 3$  hematologic toxicities occurred only in the bevacizumab plus pemetrexed arm. There were no cases of grade  $\geq 3$  pulmonary hemorrhage in either study arm. There were 41 deaths in the bevacizumab alone

**Table 2.** Summary of Adverse Events by Type and Phase of Onset

Adverse Event	Safety Population (n = 373)				Bevacizumab (n = 120)				Bevacizumab Plus Pemetrexed (n = 125)			
	Any Time		Maintenance		Any Time		Maintenance		Any Time		Maintenance	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Any grade*												
Hematologic	123	33.0	31	8.3	43	35.8	8	6.7	45	36.0	23	18.4
Nonhematologic	356	95.4	217	58.2	116	96.7	102	85.0	122	97.6	115	92.0
Most common†												
Nausea	197	52.8	43	11.5	73	60.8	14	11.7	77	61.6	29	23.2
Hypertension	122	32.7	49	13.1	44	36.7	22	18.3	55	44.0	27	21.6
Asthenia	101	27.1	27	7.2	43	35.8	10	8.3	32	25.6	17	13.6
Grade $\geq 3$ *												
Hematologic	52	13.9	13	3.5	17	14.2	0	0.0	18	14.4	13	10.4
Neutropenia	33	8.8	7	1.9	12	10.0	0	0.0	12	9.6	7	5.6
Anemia	11	2.9	4	1.1	1	0.8	0	0.0	5	4.0	4	3.2
Febrile neutropenia	3	0.8	1	0.3	1	0.8	0	0.0	1	0.8	1	0.8
Thrombocytopenia	1	0.3	0	0.0	1	0.8	0	0.0	0	0.0	0	0.0
Nonhematologic	190	50.9	65	17.4	43	35.8	26	21.7	62	49.6	39	31.2
Fatigue	9	2.4	5	1.3	3	2.5	2	1.7	4	3.2	3	2.4
Asthenia	6	1.6	0	0.0	2	1.7	0	0.0	0	0.0	0	0.0
Most common†												
Neutropenia	33	8.8	7	1.9	12	10.0	0	0.0	12	9.6	7	5.6
Hypertension	30	8.0	9	2.4	8	6.7	3	2.5	20	16.0	6	4.8
Pulmonary embolism	15	4.0	3	0.8	3	2.5	2	1.7	2	1.6	1	0.8
Serious*												
Hematologic	17	4.6	2	0.5	2	1.7	0	0.0	2	1.6	2	1.6
Nonhematologic	133	35.7	37	9.9	25	20.8	16	13.3	41	32.8	21	16.8
Most common†												
Pulmonary embolism	14	3.8	3	0.8	3	2.5	2	1.7	2	1.6	1	0.8
Pneumonia	11	2.9	2	0.5	1	0.8	0	0.0	7	5.6	2	1.6
Neutropenia	7	1.9	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0

\*Percentages of patients experiencing the event are reported.

†Defined as an adverse event of the specified type (any grade, grade  $\geq 3$ , or serious) occurring with the highest frequency in the safety population at any on-study time (induction, maintenance, or follow-up).

arm and 33 deaths in the bevacizumab plus pemetrexed arm, most (88% and 79%, respectively) resulting from PD.<sup>20</sup> There were no drug-related deaths during maintenance.

## DISCUSSION

Recent advances in NSCLC treatment include agents that target specific mutations,<sup>21–24</sup> with benefits largely limited to corresponding patient subgroups. These, however, constitute a small minority of patients.<sup>23,25–28</sup> For most patients with advanced NSCLC who lack these mutations, optimizing treatment options during induction and maintenance remains a priority. AVAPERL provides important comparative data from two continuation maintenance regimens.

In the induction phase, treatment with four cycles of bevacizumab plus cisplatin plus pemetrexed was associated with a high rate of disease control. In the maintenance phase, bevacizumab plus pemetrexed resulted in an approximate doubling of PFS, which in absolute terms translated into approximately 3 months. An exploratory analysis suggested that the PFS advantage was independent of patient age, ECOG PS, smoking history, or response to induction. The larger percentage of patients in the bevacizumab alone arm proceeding to second-line therapies may reflect the shorter interval to PD in that arm. AVAPERL was not powered for OS, and the number of OS events was small at the time of this analysis; however, the data may suggest a trend toward improved OS for patients in the bevacizumab plus pemetrexed arm.

The patients in our trial were not selected by underlying genotype, but as a caveat, they had achieved SD or PR after induction therapy. Therefore, this population represents a broad but not all-inclusive population compared with those selected for targeted agents, as in the EORTC (European Randomised Trial of Tarceva Versus Chemotherapy) study, where the median PFS was 9.4 months for patients with *EGFR*-mutated tumors who were treated with erlotinib.<sup>23</sup> Keeping in mind the uncertainties involved in cross-trial comparisons, including differences in trial populations (eg, exclusion of patients with ECOG PS 2 or CNS metastases other than treated, stable brain metastases in PARAMOUNT),<sup>29</sup> median PFS values in both AVAPERL arms (bevacizumab alone: 3.7 months; 95% CI, 3.1 to 4.8 months; bevacizumab plus pemetrexed: 7.4 months; 95% CI, 6.4 to 8.8 months) were similar to or exceeded the 4.1- (95% CI, 3.2 to 4.6 months) and 4.3-month (95% CI, 4.1 to 4.7 months) values reported for single-agent pemetrexed after induction with<sup>11</sup> or without<sup>10</sup> pemetrexed, respectively. Although AVAPERL lacked a pemetrexed alone arm to allow for direct comparison with this maintenance, comparative data for the two AVAPERL arms support the benefit of maintenance therapy with the combination of bevacizumab and pemetrexed relative to bevacizumab alone in patients with advanced nonsquamous NSCLC.

Toxicities observed in AVAPERL were as expected (eg, neutropenia in patients treated with pemetrexed; hypertension in those treated with bevacizumab). AEs were noticeably more frequent in the bevacizumab plus pemetrexed arm during the maintenance phase. Longer exposure to maintenance treatment likely accounts for some of the increases in AEs and, potentially, the study discontinuation because of AEs that were seen in this arm. Examination of the safety analysis suggests that differences in toxicities between arms may

largely be the result of toxicities commonly attributed to chemotherapy, including nausea and neutropenia.

Ongoing trials should further elucidate outcomes for maintenance bevacizumab plus pemetrexed. ECOG 5508 compares maintenance with bevacizumab alone, bevacizumab plus pemetrexed, and pemetrexed alone.<sup>30</sup> PointBreak evaluates current standard-of-care therapy with bevacizumab plus carboplatin plus paclitaxel (defined as four cycles), followed by bevacizumab continuation maintenance, compared with bevacizumab plus carboplatin plus pemetrexed followed by continuation maintenance with bevacizumab plus pemetrexed.<sup>31</sup> NCT00948675 compares induction treatment with bevacizumab plus carboplatin plus paclitaxel, followed by bevacizumab maintenance with induction treatment with pemetrexed plus carboplatin, followed by continuation maintenance with pemetrexed.<sup>32</sup>

In summary, maintenance therapy with the combination of bevacizumab and pemetrexed was associated with a significant PFS benefit relative to maintenance bevacizumab alone in an unselected population of patients with advanced nonsquamous NSCLC who had not experienced PD after induction therapy with bevacizumab, cisplatin, and pemetrexed.

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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**Table A1.** Median PFS Values From Phase III First-Line Maintenance Trials in Advanced or Metastatic NSCLC

Study	First-Line Induction Regimen	Inclusion Criteria		Induction Population Excluded From Maintenance (%)	Median PFS From Randomization by Maintenance Arm (months)
		ECOG PS	Squamous Histology Allowed?		
JMEN <sup>10</sup>	N/A*	0-1	Yes	N/A*	Placebo: 2.60 Pemetrexed: 4.30
ATLAS <sup>†</sup>	4 cycles of bevacizumab (15 mg/kg) + Pt-doublet chemotherapy	0-1	Yes	33.8	Bevacizumab + placebo: 3.71 Bevacizumab + erlotinib: 4.76
SATURN <sup>‡</sup>	4 cycles of Pt-doublet chemotherapy	0-1	Yes	54.4	Placebo: 2.55 Erlotinib: 2.83
IFCT-GFPC 0502 <sup>§</sup>	4 cycles of cisplatin + gemcitabine	0-1	Yes	44.4	Observation: 1.90 Gemcitabine: 3.80 Erlotinib: 2.90
PARAMOUNT <sup>11</sup>	4 cycles of cisplatin (75 mg/m <sup>2</sup> ) + pemetrexed (500 mg/m <sup>2</sup> )	0-1	No	42.6	Placebo: 2.80 Pemetrexed: 4.10
AVAPERL	4 cycles of cisplatin (75 mg/m <sup>2</sup> ) + pemetrexed (500 mg/m <sup>2</sup> ) + bevacizumab (7.5 mg/kg)	0-2	No	32.2	Bevacizumab: 3.70 Bevacizumab + pemetrexed: 7.40

Abbreviations: ECOG, Eastern Cooperative Oncology Group; N/A, not applicable; NSCLC, non-small-cell lung cancer; PFS, progression-free survival; PS, performance status; Pt, platinum.

\*Patients were enrolled after induction.

<sup>†</sup>Miller VA, et al: J Clin Oncol 27:407s, 2009 (suppl; abstr LBA8002).

<sup>‡</sup>Cappuzzo F, et al: Lancet Oncol 11:521-529, 2010.

<sup>§</sup>Perol M, et al: J Clin Oncol 28:540s, 2010 (suppl; abstr 7507).