MO22089 AVAPERL
SYNOPSIS CLINICAL STUDY REPORT
RESEARCH REPORT [redacted]

Synopsis Clinical Study Report – Study MO22089 – Multiple oral dose study to assess efficacy, safety, and quality of life of the combination of bevacizumab and pemetrexed as maintenance therapy versus bevacizumab alone, after first-line chemotherapy with cisplatin/pemetrexed and bevacizumab.

Date of Report:	April 30, 2012
Study Sponsor(s):	F. Hoffmann-La Roche Ltd.
Study Dates:	August 17, 2009 to May 3, 2011
Trial Phase:	III
Indication:	Non-Small Cell Lung Cancer
Name of Principal Investigator:	**Affiliation:**
[redacted]	[redacted] France

Personnel Responsible for Clinical and Statistical Analyses:

[redacted]	
F. Hoffmann-La Roche Ltd	Basel, Switzerland
[redacted]	
F. Hoffmann-La Roche Ltd	Basel, Switzerland

GCP Compliance: This study was conducted in accordance with GCP guidelines.

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COMPANY: F. Hoffmann-La Roche Ltd.	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF FINISHED PRODUCT: AVASTIN®	
NAME OF ACTIVE SUBSTANCES: bevacizumab, pemetrexed, cisplatin	

TITLE OF THE STUDY / REPORT No. / DATE OF REPORT	Open-label study of bevacizumab maintenance therapy (AVASTIN®) with or without pemetrexed after a first-line treatment chemotherapy with bevacizumab-cisplatin-pemetrexed in patients with advanced, metastatic or recurrent nonsquamous non–small cell lung cancer (NSCLC). Report [redacted]. April 30, 2012. Because these data will not be used for registrational purposes the synopsis format has been used for this report.

INVESTIGATORS / CENTERS AND COUNTRIES

France:

[redacted]

Germany:

[redacted]

[redacted]

Greece:

[redacted]

Italy:

[redacted]

Republic of Korea:

[redacted]

Netherlands:

[redacted]

[redacted]

Russian Federation:

[redacted]

Spain:

[redacted]

Sweden:

[redacted]

Switzerland:

[redacted]

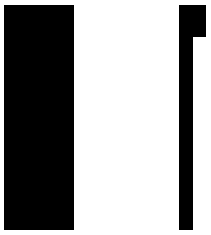
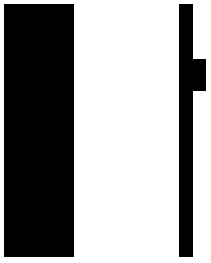
Turkey:

[redacted]

United Arab Emirates:

[redacted]

CONFERENCE PRESENTATIONS	Ahn M, Gervais R, Mezger J, et al: AVAPERL (MO22089)—Interim safety of maintenance bevacizumab + pemetrexed in patients with advanced nonsquamous non-small cell lung cancer (nsNSCLC) after first-line bevacizumab-cisplatin-pemetrexed treatment. Presented at the European Multidisciplinary Cancer Congress, Stockholm, Sweden, September 23–27, 2011 (poster 9112). Barlesi F, de Castro J, Dvornichenko V, et al: AVAPERL (MO22089): Final efficacy outcomes for patients with advanced nonsquamous non-small cell lung cancer (nsNSCLC) randomised to continuation maintenance with bevacizumab or bevacizumab + pemetrexed after first line bevacizumab-cisplatin-pemetrexed treatment. Presented at the European Multidisciplinary Cancer Congress, Stockholm, Sweden, September 23–27, 2011 (abstract LBA34). Barlesi F, Scherpereel A, Gervais R, et al: AVAPERL1 (MO22089): maintenance (mtc) bevacizumab (bev) with or without pemetrexed (pem) in patients (pts) with advanced non-squamous non-small cell lung cancer (nsNSCLC) treated with first-line (1L) bev-cisplatin (cis)-pem: interim safety data. J Clin Oncol. 2011;29 (suppl; abstr 7562). Barlesi F, Pazzola A, Gorbunova V, et al: Maintenance bevacizumab (Bv) with or without pemetrexed (pem) following first-line Bv-cisplatin (cis)-pem in patients (pts) with advanced non-squamous non-small cell lung cancer (NSCLC): preliminary safety data from AVAPERL1 (MO22089). Ann Oncol. 2010;21:viii144 (abstr 430P). Rittmeyer A, Chouaid C, Kim J-H, et al: An analysis of health-related quality of life in patients with non-squamous non-small-cell lung cancer receiving bevacizumab versus bevacizumab plus pemetrexed for maintenance therapy in AVAPERL. The European Multidisciplinary Cancer Congress, Stockholm, Sweden, September 23–27, 2011 (poster 9076).
MANUSCRIPTS	Barlesi F, Scherpereel A, Rittmeyer A, et al: A randomized phase III trial of maintenance bevacizumab with or without pemetrexed in advanced nonsquamous non-small cell lung cancer: AVAPERL (MO22089). Manuscript submitted to J Clin Oncol: February 14, 2012. Rittmeyer A, Gorbunova V, Vikström A, Scherpereel A, Kim J-H, Ahn M-J, Chella A, Chouaid C, Campbell A, Barlesi F. Health-related quality of life in patients with advanced nonsquamous non-small cell lung cancer receiving bevacizumab or bevacizumab-plus-pemetrexed maintenance therapy in AVAPERL (M)22089). Manuscript in preparation.
PERIOD OF TRIAL	First Patient In: August 17, 2009 Last Patient Out: May 3, 2011 Last Centre Closed: May 2012 CLINICAL PHASE III
OBJECTIVES	<u>Primary</u> • To assess the efficacy, measured by progression-free survival (PFS), of the combination of bevacizumab and pemetrexed as maintenance therapy versus bevacizumab alone, after first-line chemotherapy with cisplatin/pemetrexed and bevacizumab. <u>Secondary</u> • To assess the efficacy of bevacizumab in combination with pemetrexed versus bevacizumab alone as maintenance therapy, measured by response rates, disease control rates, duration of response, and overall

	survival (OS). • To assess the safety of the combination of bevacizumab and pemetrexed as first-line treatment and in maintenance therapy. • To assess quality of life (QOL) during maintenance therapy comparing bevacizumab in combination with pemetrexed versus bevacizumab alone.
STUDY DESIGN	Open-label, randomized, multicenter phase III study. Eligible patients received bevacizumab + chemotherapy for 4 cycles. If patients had a response to treatment, defined as complete response (CR), partial response (PR), or stable disease (SD) per the Response Evaluation Criteria in Solid Tumors (RECIST v1.1), they were randomized to either bevacizumab maintenance therapy or bevacizumab + pemetrexed maintenance therapy until disease progression.
NUMBER OF PATIENTS	Enrollment was planned for approximately 362 patients. Further details are described in the statistical method section.
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	A diagnosis of locally advanced (stage IIIb with supraclavicular lymph node metastases or malignant pleural or pericardial effusion), metastatic or recurrent nonsquamous NSCLC was required. Eligible patients had ≥1 unidimensionally measurable lesion meeting RECIST 1.1, an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 2, adequate hematologic, liver, and renal function, and age ≥18 years.
TRIAL DRUG (BATCH) NO.	Bevacizumab 100 mg: Batch No. No. of shipments  Bevacizumab 400 mg Batch No. No. of shipments 
REFERENCE DRUG (BATCH) NO.	Pemetrexed 500 mg: Batch No. No. of shipments  Cisplatin was not provided by the Sponsor.

DOSE / ROUTE / REGIMEN / DURATION	First part (induction phase) All patients were to receive 4 cycles of the following treatment, administered every 21 days (3 weekly cycles [q3w]): • Bevacizumab: 7.5 mg/kg on day 1, intravenously (IV) • Cisplatin: 75 mg/m^2 on day 1, IV • Pemetrexed*: 500 mg/m^2 on day 1, IV Second part (maintenance phase) Responding patients (defined as obtaining a CR/PR/SD, after 4 cycles) were randomized (1:1) to 1 of the following: • Arm A: bevacizumab 7.5 mg/kg IV • Arm B: bevacizumab 7.5 mg/kg IV in combination with pemetrexed* 500 mg/m² IV on day 1 of each cycle (q3w), until disease progression, withdrawal of consent, unacceptable toxicity, or death The first cycle of maintenance therapy had to be administered a maximum of 4 weeks after the fourth cycle of induction therapy. *Pemetrexed-treated patients received standard supplementation with folic acid orally (350 to 1000 µg daily), vitamin B_{12} intramuscularly (1000 µg every 3 cycles), and dexamethasone prophylaxis orally (4 mg twice a day) on days −1, 1, and 2 of each cycle.
CRITERIA FOR EVALUATION	
EFFICACY	Disease and tumor assessments, their evaluation according to RECIST (v1.1), and patients' survival status were recorded in the electronic case report forms (eCRF) to assess efficacy. Tumor assessments were scheduled at baseline, before cycle 3 of induction therapy, before randomization, after cycle 2 of maintenance therapy and thereafter every 3 cycles, at progression, and every 3 month during follow-up, as well at the final study visit. Primary and secondary end points are described in the Statistical Methods section. Efficacy end points based on tumor assessments in this protocol were modified to reflect clinical outcomes as measured from the time of first induction rather than from the time of randomization for reasons described below. Reason for change in end point definition When the study completed recruitment, it was realized that the available data did not support the study objectives regarding the primary end point defined by the protocol (PFS from randomization as evaluated by RECIST). The key issue was that tumor assessment performed after induction phase (at the time of randomization) was not used as the new baseline for the RECIST evaluation. When this was discovered, the majority of patients had already been randomized. All tumor response evaluations performed during the maintenance phase used the baseline tumor assessment performed prior to the induction phase (at the time of screening) as the comparator. Because of this, tumor response to maintenance treatment according to RECIST cannot be analyzed in this study. Therefore, the reference point of the primary analyses was changed and some secondary end points were adapted. The PFS analysis from the date of randomization was analyzed in a sensitivity analysis. The statistical report describes the changes to the planned analyses in detail.
QUALITY OF LIFE	QOL using the European Organization for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire–Cancer 30 (QLQ-C30)/QLQ–Lung Cancer 13 (LC13) questionnaire was assessed at each of the following time points: baseline; before cycle 3 was administered; response assessment; before cycle 1 of the maintenance phase was administered and then every 2 cycles; each follow-up visit; final visit; and in cases of premature discontinuation of the study.

SAFETY	All assessments were scheduled as indicated in the assessment table. Additional assessments were to be performed as clinically indicated. All adverse events (AEs) were assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTC-AE) criteria (v3.0). The incidence of serious AEs (SAEs) and non-SAEs that were related to bevacizumab or to pemetrexed were determined. Additional information about AEs of special interest (serious and nonserious), such as hypertension, wound-healing complications, gastrointestinal perforations, arterial and venous thromboembolic events, bleedings with a focus on hemoptysis, CNS bleeding, and sigmoiditis, were captured. The safety profile was assessed by proportion of patients experiencing at least 1 AE, 1 SAE, or 1 AE of special interest by treatment arm and toxicity category. A Data and Safety Monitoring Board (DSMB) was assigned to overview the safety of the patients.
STATISTICAL METHODS	The study was originally designed for PFS estimation from time of randomization. <u>Sample size considerations</u> Assuming the monthly accrual for this study was about 20 patients and the distribution of PFS events was exponential, a total of 362 patients needed to be recruited over an 18-month period. It was assumed that 10% of patients would not be assessable for response after the 4 cycles of induction (~ 326 patients remaining), and that 70% of the remaining patients would achieve a CR, PR, or SD (~228 patients). A total of 228 patients were expected to be randomized in the maintenance phase, resulting in 210 events during a total trial period of 27 months. Assuming a median time to disease progression or death of 15 weeks for the bevacizumab arm and 22.5 weeks for the bevacizumab-plus-pemetrexed arm (corresponding to a hazard ratio [HR] of 0.68), there was an ~80% power of the stratified log-rank test to detect the stated HR with a 2-sided alpha level of 0.05. The study was not powered to detect statistical differences in OS. For efficacy analysis reporting, patients were assigned to the group according to randomization. Efficacy analyses were performed on the intent-to-treat population. For safety analysis reporting, patients were assigned to the group according to the treatments they actually received. The safety population included all screened patients who received at least 1 dose of any study treatment. <u>Primary end point (modified)</u> PFS was defined as the period from the date of first induction treatment until the earlier date of the first disease progression or death due to any cause. Patients who had neither progressed nor died at the date of clinical cutoff, who withdrew from the study, were lost to follow-up, or were without documented disease progression were censored at the date of the last available tumor assessment when they were known to have not progressed. Patients without postbaseline tumor assessment were censored at the date of first induction treatment. An exploratory efficacy analysis of PFS from the date of randomization was also performed. The primary end point, PFS, was evaluated using time-to-event methods. Kaplan-Meier estimates of the quartiles (25% quartile, median, 75% quartile) were given for each treatment arm, and 95% confidence intervals (CI) for the medians were calculated. Also, the number of patients with events, the number of censored patients, hazard ratios with corresponding 95% CIs using stratified and unadjusted Cox regression models, and *P* values for stratified and unadjusted log-rank tests were summarized. The estimates of PFS at 6, 12 and 18 months with corresponding 95% CIs were presented. The stratification variables were gender, smoking status, and the patients' response that was assessed during induction phase and recorded

at randomization. The stratified analyses were the main analysis for the primary end point.

Secondary efficacy end points

OS was assessed from the date of first induction treatment until the date of death. Patients who had not died at the date of data cutoff or patients who withdrew from the study or were lost to follow-up were censored at the last date at which they were known to be alive (ie, the date of last follow-up or the date of last study drug administration or any on-treatment assessment, if there were no follow-up assessments). OS was also assessed from the date of randomization until the date of death. This end point was analyzed using the same methods as the primary end point.

Best overall response (BOR) was assessed for patients with measurable disease at baseline (ie, patients who had at least 1 target lesion at baseline). This secondary end point was summarized by number and percentage of responders, ie, patients who achieved a BOR of CR or PR. The difference in response, the corresponding 95% Hauck-Anderson CI and a 2-sided Cochran-Mantel-Haenszel chi-squared test stratified by randomization stratification variables were presented for this end point. Also, 95% Clopper-Pearson CI was included for the responses rate within the same treatment arm.

Disease control rates (ie, patients with CR, PR, or SD) were analyzed using same methods as BOR analyses.

Duration of response and duration of disease control were analyzed using the same methods as the primary end point.

There was no interim efficacy analysis, but regular safety reviews of data were performed by the DSMB.

GCP COMPLIANCE	This trial was conducted in accordance with the principles of ICH GCP and local applicable regulations. Three (CRTN [redacted] in October 2010, [redacted] in December 2010 and [redacted] in September 2010) investigational sites were audited. In 2 of these 3 sites, major findings of noncompliance were observed that prompted the implementation of corrective and preventive actions. These findings did not negatively impact the overall outcome of the trial.
METHODOLOGY	Before any study-specific examinations were performed, the patients who were willing to participate in the study gave written informed consent. A screening examination was performed between 28 days and 1 day before the first dose of treatment (7 days for serum pregnancy test in female patients), which included the following procedures (unless the procedures had already been conducted during this time period as part of the patient's routine clinical care): eligibility, medical history, physical examination, ECOG PS, blood sampling for serum pregnancy test and assessment of laboratory parameters, urinalysis, tumor assessment, concomitant medication, AEs, SAEs, and QOL. Patients who fulfilled all the inclusion and none of the exclusion criteria were included in the study. The first part of the study (induction phase) consisted of 4 cycles (21-day cycles) of cisplatin, pemetrexed, and bevacizumab. Patients with a response to treatment, defined as CR, PR, or SD, were included in the second part of the study (maintenance phase), were randomized at a 1:1 ratio to either bevacizumab or bevacizumab plus pemetrexed, and were followed up until progressive disease. Patients were stratified by gender, smoking status, and response at randomization. In the induction phase, patients received bevacizumab (7.5 mg/kg IV), cisplatin (75 mg/m^2 IV), and pemetrexed (500 mg/m^2) on day 1 of each of 21-day cycle (4 cycles). Pemetrexed was administered first, over the course

of 10 minutes. Cisplatin was administered 30 minutes later, over the course of 2 hours. The initial dose of bevacizumab was given over 90 minutes. If bevacizumab was well tolerated, subsequent bevacizumab infusions could be given over 60 minutes and, eventually, 30 minutes. Pemetrexed-treated patients (all patients during induction and those receiving bevacizumab-plus-pemetrexed maintenance) received standard supplementation with folic acid (350–1000 µg QD orally), and vitamin B_{12} (1000 µg IM once each cycle) starting 1 to 2 weeks before the first infusion, and dexamethasone (4 mg BID orally) prophylaxis on days −1, 1, and 2 of each cycle throughout the study.

Bevacizumab dose modifications were not allowed, but treatment could be delayed or omitted for 1 to 2 consecutive cycles (up to 42 days) if necessary. If a patient's weight changed by >10% during the course of the study, the dose of bevacizumab was recalculated. In cases of hematologic toxicity, treatment with cisplatin and pemetrexed could be delayed for up to 3 weeks until the day 1 absolute neutrophil count (ANC) was $\geq 1.5\times10^9$/L and platelet count was $>100\times10^9$/L. Pemetrexed and cisplatin doses could then be reduced to 75% or 50% of the previous dose, depending on the ANC and platelet nadirs. In cases of grade ≥3 nonhematologic toxicities (except for alopecia and neurotoxicity), pemetrexed and cisplatin were withheld until resolution and then reduced to 75% or 50% (for grade 3–4 mucositis) of the previous doses. In the event of grade 2 neurotoxicity, the cisplatin dose was reduced by 50%; grade 3 or 4 neurotoxicity required permanent cisplatin discontinuation.

Before each cycle and at progression, patients underwent a physical examination and blood sampling for assessment of laboratory parameters and urinalysis. Their ECOG PS was evaluated. Their weight and vital signs were measured and their concomitant medications were reported in the eCRF. Tumor response was assessed at baseline and at defined time points as described previously. All tumor assessments used RECIST v1.1. AEs were collected at each cycle and at every 3-month follow-up. AEs were to be reported up to 28 days after bevacizumab infusion, and those of special interest were to be reported up to 6 months after the last bevacizumab infusion (but not beyond clinical cutoff). Related SAEs were to be reported regardless of the time elapsed from the last bevacizumab infusion. The AEs were assessed using the NCI CTC-AE v3.0. AEs were coded using the Medical Dictionary for Regulatory Activities. QOL questionnaires were completed as described previously.

After progression of disease, patients were followed up with for survival, and subsequent therapies were recorded. The trial was conducted according to relevant Roche standard operating procedures.

DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Between August 2009 and July 2010, 414 patients were screened at 81 centers in 11 countries (Figure 1). Thirty-eight patients were excluded for not meeting the eligibility criteria, for declining to participate, or for other reasons. Of the 376 patients enrolled in the study, 3 received no induction phase treatment and were excluded from the safety analysis but were included in the efficacy analysis (intent-to-treat). Following induction therapy, 253 patients were randomized to maintenance therapy and 120 patients were not randomized to maintenance because of discontinuations related to an AE, progressive disease, withdrawal of consent, or other reasons. A total of 125 patients were allocated to bevacizumab maintenance, and 128 patients were allocated to bevacizumab-plus-pemetrexed maintenance. Five patients and 3 patients, respectively, in these arms did not receive maintenance treatment.

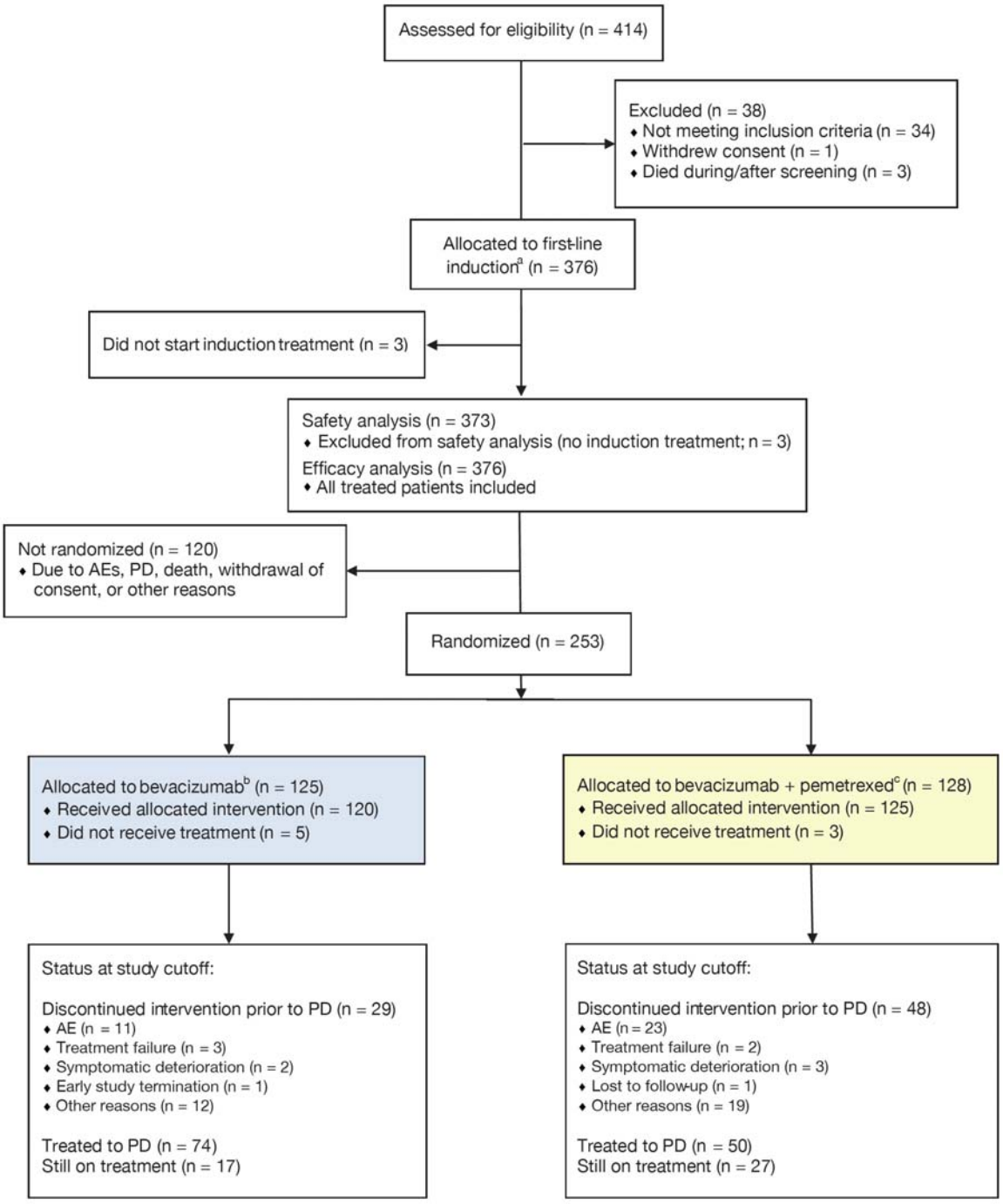


Figure 1. AVAPERL CONSORT diagram and treatment schema. AE, adverse event; PD, progressive disease.

DEMOGRAPHICS AND BASELINE CHARACTERISTICS (CONT.)

Patient and disease characteristics at baseline for induction were generally similar between both maintenance arms (Table 1). Similar percentages of patients in the bevacizumab and bevacizumab + pemetrexed arms were male (56.7% vs 57.6%, respectively), and ≥65 years (29.2% vs 29.6%, respectively), Slightly more patients had ECOG PS of 0 in arm B (arm A 42.7% vs arm B 52.4%) However at the time of randomization, patient characteristics, including ECOG PS (0/1/2 31.7%/62.5%/5.8% and 33.7%/64.4%/1.9% in the bevacizumab and bevacizumab-plus-pemetrexed arms, respectively), were similar between treatment arms.

Table 1. Summary of Patient and Disease Characteristics at Induction Baseline

	No Maintenance Trt N=128	Maintenance Trt Arm A N=120	Maintenance Trt Arm B N=125	Total N=373
Age [years] at screening				
N	128	120	125	373
Mean (std)	59.5 (10.16)	59.7 (7.58)	59.1 (8.83)	59.5 (8.92)
Median	61.0	60.0	60.0	60.0
Q1 - Q3	52.0 - 66.0	55.0 - 65.0	53.0 - 65.0	53.0 - 66.0
Min - Max	27 - 83	41 - 75	34 - 76	27 - 83
Missing	0	0	0	0
Age (categorical)				
<65 years	84 (65.6%)	85 (70.8%)	88 (70.4%)	257 (68.9%)
>=65 years	44 (34.4%)	35 (29.2%)	37 (29.6%)	116 (31.1%)
Age (categorical)				
<70 years	105 (82.0%)	109 (90.8%)	107 (85.6%)	321 (86.1%)
>=70 years	23 (18.0%)	11 (9.2%)	18 (14.4%)	52 (13.9%)
Gender				
Male	80 (62.5%)	68 (56.7%)	72 (57.6%)	220 (59.0%)
Female	48 (37.5%)	52 (43.3%)	53 (42.4%)	153 (41.0%)
Race				
White	83 (64.8%)	65 (54.2%)	76 (60.8%)	224 (60.1%)
Black	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Asian	6 (4.7%)	10 (8.3%)	18 (14.4%)	34 (9.1%)
Other	2 (1.6%)	2 (1.7%)	0 (0.0%)	4 (1.1%)
Not reported #	37 (28.9%)	43 (35.8%)	31 (24.8%)	111 (29.8%)
Height [cm]				
N	128	120	125	373
Mean (std)	170.1 (9.67)	168.6 (8.93)	169.4 (8.35)	169.4 (9.00)
Median	170.0	168.5	169.0	169.0
Q1 - Q3	164.0 - 176.0	162.0 - 175.0	163.0 - 175.0	163.0 - 175.0
Min - Max	145 - 195	150 - 194	150 - 194	145 - 195
Missing	0	0	0	0
ECOG performance status at screening				
0: Normal activity	51 (41.5%)	50 (42.7%)	65 (52.4%)	166 (45.6%)
1: Symptomatic but ambulatory self-care	70 (56.9%)	65 (55.6%)	57 (46.0%)	192 (52.7%)
2: Ambulatory more than 50% of the time	2 (1.6%)	2 (1.7%)	2 (1.6%)	6 (1.6%)
3: Ambulatory 50% or less of time, nursing care needed	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
4: Bedridden, may need hospitalization	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	5	3	1	9

Weight [kg] 6 months before screening				
N	114	106	93	313
Mean (std)	74.7 (14.37)	74.0 (16.03)	74.4 (15.43)	74.3 (15.22)
Median	75.3	71.0	73.0	73.0
Q1 - Q3	64.0 - 85.0	64.0 - 82.0	64.0 - 81.0	64.0 - 82.0
Min - Max	37 - 116	44 - 120	42 - 133	37 - 133
Missing	14	14	32	60
Weight [kg] at screening				
N	128	120	125	373
Mean (std)	71.2 (14.56)	72.9 (15.90)	72.0 (15.38)	72.0 (15.25)
Median	71.0	70.2	70.0	70.3
Q1 - Q3	61.5 - 80.0	64.0 - 82.5	63.0 - 78.0	62.0 - 81.0
Min - Max	35 - 112	42 - 120	42 - 133	35 - 133
Missing	0	0	0	0
Weight: absolute change from 6 months before [kg]				
N	114	106	93	313
Mean (std)	-3.3 (4.67)	-1.8 (4.73)	-1.4 (3.40)	-2.2 (4.42)
Median	-2.0	0.0	0.0	0.0
Q1 - Q3	-6.0 - 0.0	-4.0 - 0.0	-2.7 - 0.0	-5.0 - 0.0
Min - Max	-20 - 15	-16 - 11	-13 - 7	-20 - 15
Missing	14	14	32	60
BSA [m²] at screening				
N	128	120	125	373
Mean (std)	1.82 (0.212)	1.82 (0.216)	1.82 (0.201)	1.82 (0.209)
Median	1.83	1.78	1.78	1.79
Q1 - Q3	1.69 - 1.96	1.68 - 1.97	1.69 - 1.93	1.68 - 1.96
Min - Max	1.3 - 2.4	1.3 - 2.5	1.4 - 2.5	1.3 - 2.5
Missing	0	0	0	0
Smoking history				
Current smoker	46 (36.2%)	30 (25.2%)	28 (22.4%)	104 (28.0%)
Past smoker	69 (54.3%)	58 (48.7%)	66 (52.8%)	193 (52.0%)
Never smoker	12 (9.4%)	31 (26.1%)	31 (24.8%)	74 (19.9%)
Missing	1	1	0	2

Race not reported for French sites due to legal restrictions.

	No Maintenance Trt N=128	Maintenance Trt Arm A N=120	Maintenance Trt Arm B N=125	Total N=373
Diagnosis at early stage				
No	120 (93.8%)	115 (95.8%)	113 (90.4%)	348 (93.3%)
Yes	8 (6.3%)	5 (4.2%)	12 (9.6%)	25 (6.7%)
Unknown	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
If diagnosed at early stage, stage of diagnosis *				
I	3 (37.5%)	2 (40.0%)	6 (50.0%)	11 (44.0%)
II	2 (25.0%)	2 (40.0%)	3 (25.0%)	7 (28.0%)
IIIa	3 (37.5%)	1 (20.0%)	3 (25.0%)	7 (28.0%)
Current stage				
IIIb	8 (6.3%)	13 (10.8%)	7 (5.6%)	28 (7.5%)
IV	120 (93.8%)	107 (89.2%)	118 (94.4%)	345 (92.5%)
Diagnosis of locally advanced or metastatic disease #				
By histology	104 (81.3%)	96 (80.0%)	100 (80.0%)	300 (80.4%)
Bronchoscopy **	55 (52.9%)	52 (54.2%)	59 (59.0%)	166 (55.3%)
Other **	49 (47.1%)	44 (45.8%)	41 (41.0%)	134 (44.7%)
By cytology	39 (30.5%)	46 (38.3%)	38 (30.4%)	123 (33.0%)
Sample FNA **	24 (61.5%)	25 (54.3%)	19 (50.0%)	68 (55.3%)
Sputum **	1 (2.6%)	0 (0.0%)	3 (7.9%)	4 (3.3%)
Pleural effusion **	7 (17.9%)	9 (19.6%)	5 (13.2%)	21 (17.1%)
Other **	7 (17.9%)	12 (26.1%)	11 (28.9%)	30 (24.4%)
Histologic subtype (pathology results)				
Adenocarcinoma	112 (87.5%)	110 (91.7%)	107 (85.6%)	329 (88.2%)
Large cell carcinoma	13 (10.2%)	9 (7.5%)	12 (9.6%)	34 (9.1%)
Bronchoaleveolar carcinoma	1 (0.8%)	0 (0.0%)	3 (2.4%)	4 (1.1%)
Mixed cell type (> 50% non-squamous)	1 (0.8%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Other	1 (0.8%)	1 (0.8%)	3 (2.4%)	5 (1.3%)
Centrally located lung tumour				
No	73 (57.0%)	77 (64.2%)	79 (63.2%)	229 (61.4%)
Yes	55 (43.0%)	43 (35.8%)	46 (36.8%)	144 (38.6%)
Cavitated tumour				
No	124 (96.9%)	113 (94.2%)	119 (95.2%)	356 (95.4%)
Yes	4 (3.1%)	7 (5.8%)	6 (4.8%)	17 (4.6%)

* Univariate statistics based on patients with diagnosis at early stage.
** Univariate statistics based on patients with histology and cytology, respectively.
# Multiple ticks possible on eCRF.

Table 2. Extent of Exposure to Cisplatin (Safety Population by Actual Treatment)

	No Maintenance Trt N=128	Maintenance Trt Arm A N=120	Maintenance Trt Arm B N=125	Total N=373
Number of cycles with administration per patient				
N	128	120	125	373
Mean (std)	2.6 (1.08)	4.0 (0.00)	4.0 (0.00)	3.5 (0.92)
Median	2.0	4.0	4.0	4.0
Q1 - Q3	2.0 - 4.0	4.0 - 4.0	4.0 - 4.0	4.0 - 4.0
Min - Max	1 - 4	4 - 4	4 - 4	1 - 4
Missing	0	0	0	0
Number of cycles with administration per patient (categorical)				
0	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
1	22 (17.2%)	0 (0.0%)	0 (0.0%)	22 (5.9%)
2	46 (35.9%)	0 (0.0%)	0 (0.0%)	46 (12.3%)
3	23 (18.0%)	0 (0.0%)	0 (0.0%)	23 (6.2%)
4	37 (28.9%)	120 (100.0%)	125 (100.0%)	282 (75.6%)

Table 3. Extent of Exposure to Bevacizumab (Safety Population by Actual Treatment)

	No Maintenance Trt N=128	Maintenance Trt Arm A N=120	Maintenance Trt Arm B N=125	Total N=373
Number of cycles with administration per patient				
N	128	120	125	373
Mean (std)	2.5 (1.11)	10.5 (4.65)	11.4 (4.74)	8.1 (5.58)
Median	2.0	9.0	11.0	7.0
Q1 - Q3	2.0 - 4.0	7.0 - 14.0	8.0 - 15.0	3.0 - 12.0
Min - Max	1 - 4	5 - 27	1 - 24	1 - 27
Missing	0	0	0	0
Number of cycles with administration per patient (categorical)				
0	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
1	27 (21.1%)	0 (0.0%)	1 (0.8%)	28 (7.5%)
2	45 (35.2%)	0 (0.0%)	0 (0.0%)	45 (12.1%)
3	21 (16.4%)	0 (0.0%)	0 (0.0%)	21 (5.6%)
4	35 (27.3%)	0 (0.0%)	0 (0.0%)	35 (9.4%)
5-9	0 (0.0%)	67 (55.8%)	54 (43.2%)	121 (32.4%)
10-14	0 (0.0%)	26 (21.7%)	34 (27.2%)	60 (16.1%)
15-19	0 (0.0%)	23 (19.2%)	29 (23.2%)	52 (13.9%)
20-24	0 (0.0%)	3 (2.5%)	7 (5.6%)	10 (2.7%)
25-29	0 (0.0%)	1 (0.8%)	0 (0.0%)	1 (0.3%)

Table 4. Extent of Exposure to Pemetrexed (Safety Population by Actual Treatment)

	No Maintenance Trt N=128	Maintenance Trt Arm A N=120	Maintenance Trt Arm B N=125	Total N=373
Number of cycles with administration per patient				
N	128	120	125	373
Mean (std)	2.6 (1.09)	4.0 (0.00)	11.6 (4.61)	6.1 (4.82)
Median	2.0	4.0	11.0	4.0
Q1 - Q3	2.0 - 4.0	4.0 - 4.0	8.0 - 15.0	4.0 - 8.0
Min - Max	1 - 4	4 - 4	5 - 24	1 - 24
Missing	0	0	0	0
Number of cycles with administration per patient (categorical)				
0	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
1	22 (17.2%)	0 (0.0%)	0 (0.0%)	22 (5.9%)
2	46 (35.9%)	0 (0.0%)	0 (0.0%)	46 (12.3%)
3	22 (17.2%)	0 (0.0%)	0 (0.0%)	22 (5.9%)
4	38 (29.7%)	120 (100.0%)	0 (0.0%)	158 (42.4%)
5-9	0 (0.0%)	0 (0.0%)	53 (42.4%)	53 (14.2%)
10-14	0 (0.0%)	0 (0.0%)	36 (28.8%)	36 (9.7%)
15-19	0 (0.0%)	0 (0.0%)	29 (23.2%)	29 (7.8%)
20-24	0 (0.0%)	0 (0.0%)	7 (5.6%)	7 (1.9%)
25-29	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 5. Duration of Follow-Up (Safety Population by Actual Treatment)

	No Maintenance Trt N=128	Maintenance Trt Arm A N=120	Maintenance Trt Arm B N=125	Total N=373
Duration of follow-up (incl. induction phase) [months]				
N	128	120	125	373
Mean (std)	6.92 (4.869)	11.00 (3.423)	11.54 (3.404)	9.78 (4.478)
Median	6.67	10.76	11.07	10.35
Q1 - Q3	2.53 - 10.83	9.40 - 13.34	9.72 - 13.93	6.67 - 13.01
Min - Max	0.1 - 19.5	3.4 - 18.8	3.8 - 19.0	0.1 - 19.5
Missing	0	0	0	0
Duration of follow-up (excl. induction phase) [months]				
N	128	120	125	373
Mean (std)	0.33 (1.713)	8.06 (3.395)	8.68 (3.438)	5.62 (4.829)
Median	0.00	7.97	8.28	6.57
Q1 - Q3	0.00 - 0.00	6.18 - 10.43	6.87 - 11.24	0.00 - 9.40
Min - Max	0.0 - 11.9	0.5 - 16.0	0.7 - 16.2	0.0 - 16.2
Missing	0	0	0	0
Follow-up assessments per patient				
N	128	120	125	373
Mean (std)	1.7 (1.61)	1.1 (0.99)	1.0 (1.07)	1.2 (1.29)
Median	1.0	1.0	1.0	1.0
Q1 - Q3	0.0 - 3.0	0.0 - 2.0	0.0 - 2.0	0.0 - 2.0
Min - Max	0 - 8	0 - 3	0 - 5	0 - 8
Missing	0	0	0	0
Follow-up assessments per patient (categorical)				
0	37 (28.9%)	41 (34.2%)	51 (40.8%)	129 (34.6%)
1	33 (25.8%)	45 (37.5%)	40 (32.0%)	118 (31.6%)
2	23 (18.0%)	20 (16.7%)	22 (17.6%)	65 (17.4%)
3	16 (12.5%)	14 (11.7%)	9 (7.2%)	39 (10.5%)
4	12 (9.4%)	0 (0.0%)	2 (1.6%)	14 (3.8%)
5	5 (3.9%)	0 (0.0%)	1 (0.8%)	6 (1.6%)
6	1 (0.8%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
8	1 (0.8%)	0 (0.0%)	0 (0.0%)	1 (0.3%)

EFFICACY RESULTS

Results are presented for stratified analyses unless otherwise specified. Following induction-phase treatment, disease control was achieved in 71.9% (269/374) of patients with measurable disease at baseline. All responses were partial. BOR based on all response assessments and other efficacy outcomes are shown in Table 6.

Primary end point (modified)

PFS events occurred in 104 (83.2%) and 81 (63.3%) patients in the bevacizumab and bevacizumab-plus-pemetrexed arms, respectively. The median PFS from first induction treatment was 6.6 months (95% CI, 6.0–7.8 months) in the bevacizumab arm and 10.2 months (95% CI, 9.1–11.7 months) in the bevacizumab-plus-pemetrexed arm, with a HR for progression of 0.50 (95% CI, 0.37–0.69; *P*<.001) using the stratified model and 0.54 (95% CI, 0.40–0.72; *P*<.001) using an unstratified model.

A subgroup analysis showed that the bevacizumab-plus-pemetrexed arm had consistently higher median PFS compared with the bevacizumab-alone arm in subgroups based on age (age <70 years: HR, 0.51; 95% CI, 0.37–0.71; *P*<.001; age ≥70 years: HR, 0.78; 95% CI, 0.35–1.77; *P*=.560), ECOG PS (ECOG PS 0: HR, 0.43; 95% CI, 0.27–0.67; *P*<.001; ECOG PS 1: HR, 0.60; 95% CI, 0.40–0.92; *P*=.018), smoking history (never-smokers: HR, 0.40; 95% CI, 0.21–0.74, *P*=.004; current/past smokers: HR, 0.59; 95% CI: 0.42–0.82; *P*=.002), and response prior to randomization (SD prior to randomization: HR, 0.64; 95% CI, 0.41–0.98; *P*=.041; PR/CR prior to randomization: HR, 0.46 [95% CI, 0.31–0.69]; *P*<.001).

AVAPERL was not powered for OS. OS events occurred in 42 (34%) and 34 (27%) patients in the bevacizumab and bevacizumab-plus-pemetrexed arms, respectively. When the database was locked after 10.9 months of median follow-up in the intent-to-treat population, the median OS from time of first induction was 15.7 months in the bevacizumab arm and had not yet been reached in the bevacizumab + pemetrexed arm, while, in an exploratory analysis, median OS from time of randomization was 12.8 months and not yet reached in these arms, respectively. 6-, 12-, and 18-month OS values are shown in Table 6.

A total of 71 (57%) and 56 (44%) patients in the bevacizumab and bevacizumab-plus-pemetrexed arms, respectively, went on to receive subsequent treatment. The most common classes of subsequent therapeutic agents were tyrosine kinase inhibitors (32% vs 28%, respectively), taxanes (26% vs 13%, respectively), surgical and medical procedures (12% vs 9%, respectively), antimetabolites (15% vs 6%, respectively), and platinum compounds (5% vs 6%, respectively). Some patients received multiple agents.

Table 6. Efficacy Outcomes With Maintenance Therapy

Outcome	Bevacizumab (n=125)	Bevacizumab + Pemetrexed (n=128)	Hazard Ratio[a] (95% CI)
PFS from induction (primary end point)[b]			
Median, months (95% CI)	6.6 (6.0–7.8)	10.2 (9.1–11.7)	0.50 (0.37–0.69); *P*<.001
At 6 months, % (95% CI)	59.9 (51.2–68.6)	83.9 (77.5–90.4)	—
At 12 months, % (95% CI)	15.6 (8.5–22.7)	37.3 (27.4–47.2)	—
BORR[c], % (95%CI)			
Partial response	50.0 (40.9–59.1)	55.5 (46.4–64.3)	
Stable disease	50.0 (40.9–59.1)	44.5 (35.7–53.6)	
Duration of response, Median, months (95% CI)	5.7 (4.9–7.2)	9.2 (6.8–10.4)	0.53 (0.34–0.84); *P*=.006
Duration of disease control Median, months (95% CI)	4.9 (3.9–5.7)	7.8 (6.8–9.7)	0.52 (0.38–0.70); *P*<.001
PFS from randomization (sensitivity analysis)[b]			
Median, months (95% CI)	3.7 (3.1–4.8)	7.4 (6.4–8.8)	0.48 (0.35–0.66); *P*<.001
OS from induction[d]			
Median, months (95% CI)	15.7 (14.3–NR)	NR	0.75 (0.47–1.20); *P*=.230
At 6 months, % (95% CI)	90.3 (85.1–95.5)	96.8 (93.7–99.9)	—
At 12 months, % (95% CI)	70.2 (61.5–78.8)	74.9 (66.9–82.9)	—
At 18 months, % (95% CI)	47.7 (31.5–64.0)	65.5 (55.0–76.1)	—
OS from randomization[d]			
Median, months (95% CI)	12.8 (11.5–NR)	NR	0.75 (0.47–1.19); *P*=.219
At 6 months, % (95% CI)	79.5 (72.4–86.7)	85.4 (79.1–91.6)	—
At 12 months, % (95% CI)	58.1 (46.4–69.8)	65.3 (54.7–75.9)	—
At 18 months, % (95% CI)	NA	NA	—

[a]Hazard ratios stratified by gender, smoking status, and BORR (complete response/partial response or stable disease) at randomization.

[b]Based on PFS events in 104 patients in the bevacizumab arm and 81 patients in the bevacizumab-plus-pemetrexed arm.

[c]Based on all response assessments.

[d]Based on OS events in 42 patients in the bevacizumab arm and 34 patients in the bevacizumab-plus-pemetrexed arm.

Complete response, partial response, or stable disease was required for patients to be eligible for randomization to a maintenance arm.

BORR, best overall response rate; CI, confidence interval; NA, not available; NR, not reached; OS, overall survival; PFS, progression-free survival.

QUALITY-OF-LIFE RESULTS

QOL was assessed using the EORTC QLQ-C30/QLQ-LC13 instruments. The QLQ-C30 has been shown to be a reliable and valid measure of the QOL of cancer patients in multicultural clinical research settings. The QLQ-LC13 module has also been shown to be a clinically valid and useful tool for assessing disease- and treatment-specific symptoms in lung cancer patients participating in clinical trials, especially when combined with the QLQ-C30. The QOL analysis was focused on questionnaires covering preinduction to maintenance (MTC) 11 time points; although data continued to be obtained through MTC 23 and subsequent follow-up, relatively few completed questionnaires (n<40) were available for these later time points. QOL analysis was based on the intent-to-treat patient population.

The percentage of patients completing and returning the QOL questionnaires in the bevacizumab and bevacizumab-plus-pemetrexed maintenance arms are shown in Table 7.

Table 7. Compliance with QOL assessments

	Bevacizumab			Bevacizumab + Pemetrexed		
	Pts on-study, no.	Distributed, no.	Completed (%)*	Pts on-study, no.	Distributed, no.	Completed (%)*
Pre-ind BL	125	121	118 (94.4)	128	126	121 (94.5)
Ind cycle 3	125	117	111 (88.8)	128	115	114 (89.1)
Pre-MTC BL	120	119	119 (99.2)	125	124	124 (99.2)
MTC cycle 3	110	73	69 (62.7)	120	87	87 (72.5)
MTC cycle 5	83	52	50 (60.2)	98	81	77 (78.6)
MTC cycle 7	56	39	38 (67.9)	75	66	64 (85.3)
MTC cycle 9	48	33	33 (68.8)	59	52	50 (84.7)
MTC cycle 11	35	25	25 (71.4)	47	39	37 (78.7)

*Percentage is based on the number of on-study patients in the arm at each time point.

BL, baseline; Ind, induction; MTC, maintenance; pts, patients.

QUALITY-OF-LIFE RESULTS (CONT.)

Mean scores for selected functional and symptom scales are also shown graphically in Figure 2 and Figure 3. All cycles with clinically relevant differences (≥10 points) from premaintenance baseline prior to specified maintenance cycles are shown in Table 8. A Forest plot of the differences between trial arms in changes of QLQ-C30 functional domain scores and global health during maintenance cycles 3 through 11 relative to premaintenance baseline scores is shown in Figure 4.

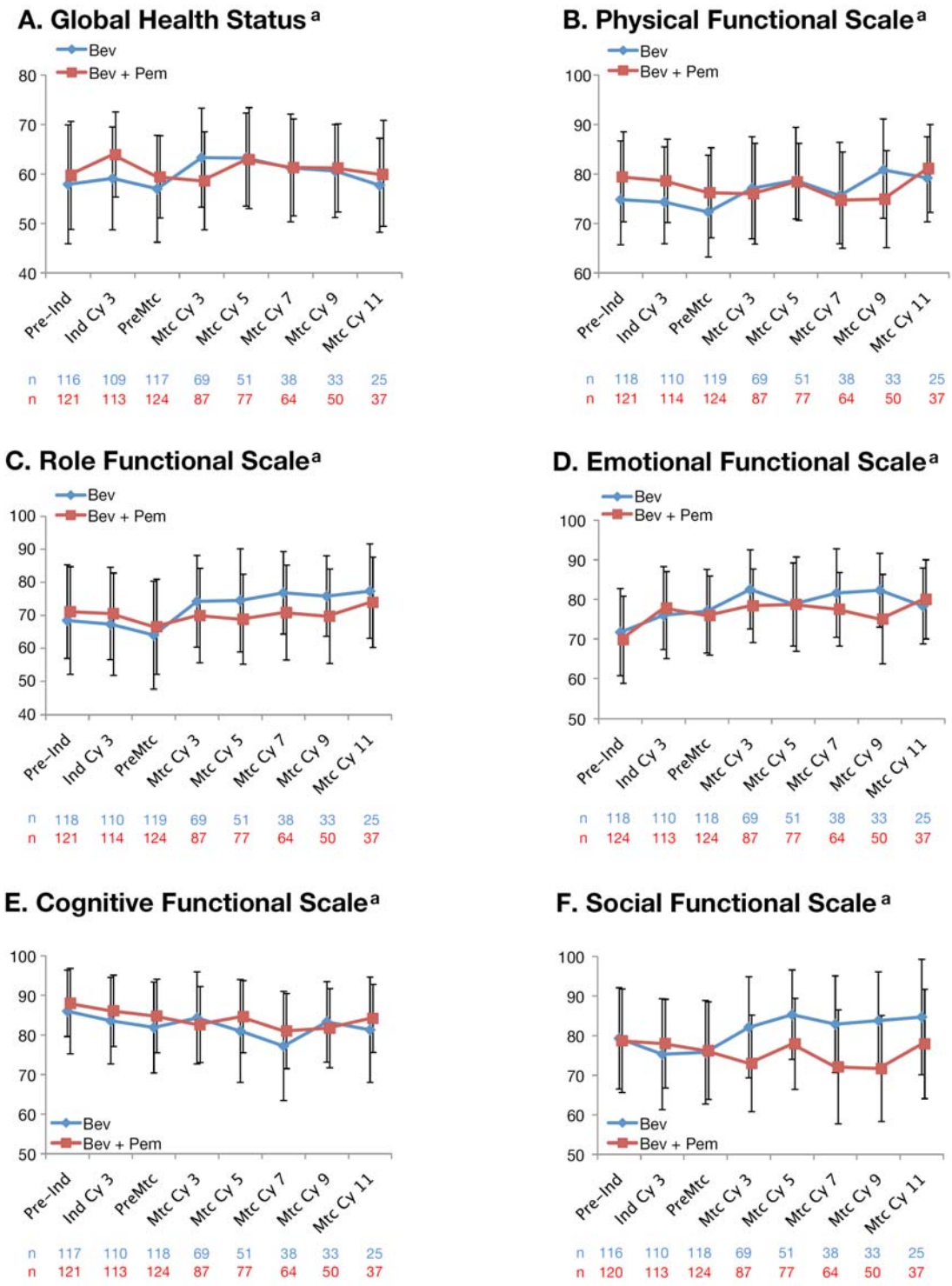


Figure 2. Mean scores for selected patient-reported EORTC functional scales in AVAPERL, showing standard deviation values.

[a]Source: European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire–Cancer 30.
Bev, bevacizumab; Cy, cycle; EORTC, European Organization for Research and Treatment of Cancer; MTC, maintenance; Pem, pemetrexed.

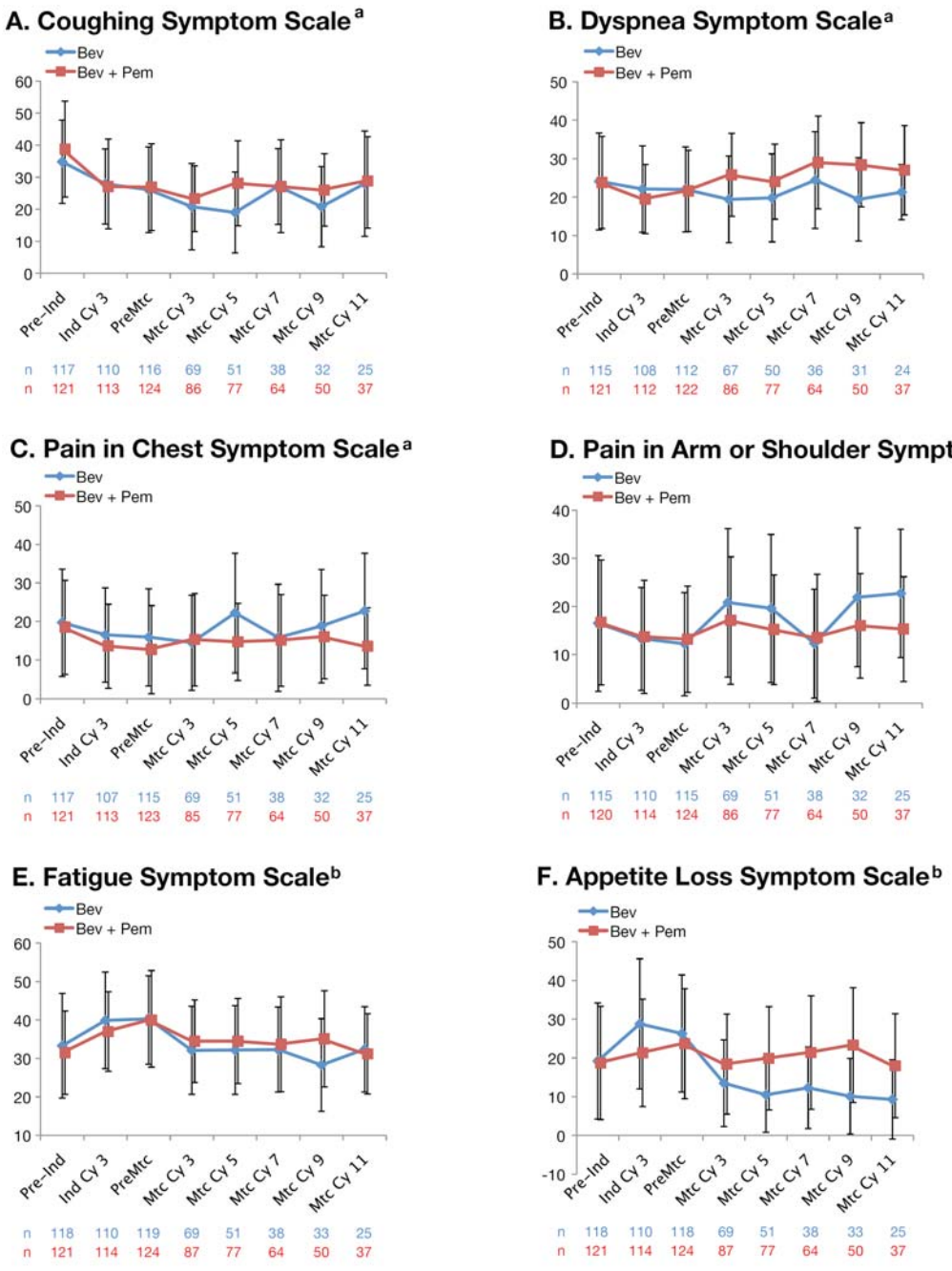


Figure 3. Mean scores for selected patient-reported EORTC functional scales in AVAPERL, showing standard deviation values.

[a]Source: European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire–Lung Cancer 13.
[b]Source: European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire–Cancer 30.
Bev, bevacizumab; Cy, cycle; EORTC, European Organization for Research and Treatment of Cancer; MTC, maintenance; Pem, pemetrexed.

Table 8. Cycles with Clinically Relevant Differences (≥10 points) from Premaintenance Baseline Prior to Specified Maintenance Cycle.

	MTC 3		MTC 5		MTC 7		MTC 9		MTC 11		Favors
	BV	BV + P	BV	BV + P	BV	BV + P	BV	BV + P	BV	BV + P	
Patients, no.	69	87	51	77	38	64	33	50	25	37	
Role functioning[a]	5.9	1.3	7.8	–1.9	18.0	–2.3	16.2	–4.7	18.7	–2.7	BV
Fatigue symptoms[a]	–7.0	–6.3	–6.1	–4.5	–11.0	–2.6	–12.8	–3.6	–8.9	–6.3	BV
Nausea/vomiting symptoms[a]	–9.1	–8.4	–10.1	–8.2	–14.5	–6.0	–20.2	–5.7	–14.7	–7.2	BV
Appetite loss symptoms[a]	–10.3	–6.1	–13.1	–3.9	–17.1	0.5	–20.8	0.0	–20.8	–2.7	BV
Constipation symptoms[a]	–7.4	–3.1	–10.5	1.7	–5.3	0.5	–5.1	2.7	–8.0	1.8	BV
Pain in arm/shoulder symptoms[b]	8.5	3.5	8.2	–1.7	0.0	–5.2	9.7	–1.3	12.5	0.0	BV+P
Alopecia symptoms[b]	2.0	1.9	–3.5	1.3	–7.9	–1.0	–12.5	–8.7	–14.7	–10.8	BV
Peripheral neuropathy symptoms[b]	–0.5	4.7	4.1	9.5	4.5	12.0	–4.3	16.7	2.8	9.9	BV

[a]Source: European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire–Cancer 30.
[b]Source: European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire–Lung Cancer 13.

Red font indicates a statistically significant difference between trial arm scores. A positive value for a functional score indicates an improvement in functional level compared with premaintenance baseline. A positive value for a symptom scale represents an improvement in symptom level compared with premaintenance baseline.

BV, bevacizumab; MTC, maintenance; P, pemetrexed

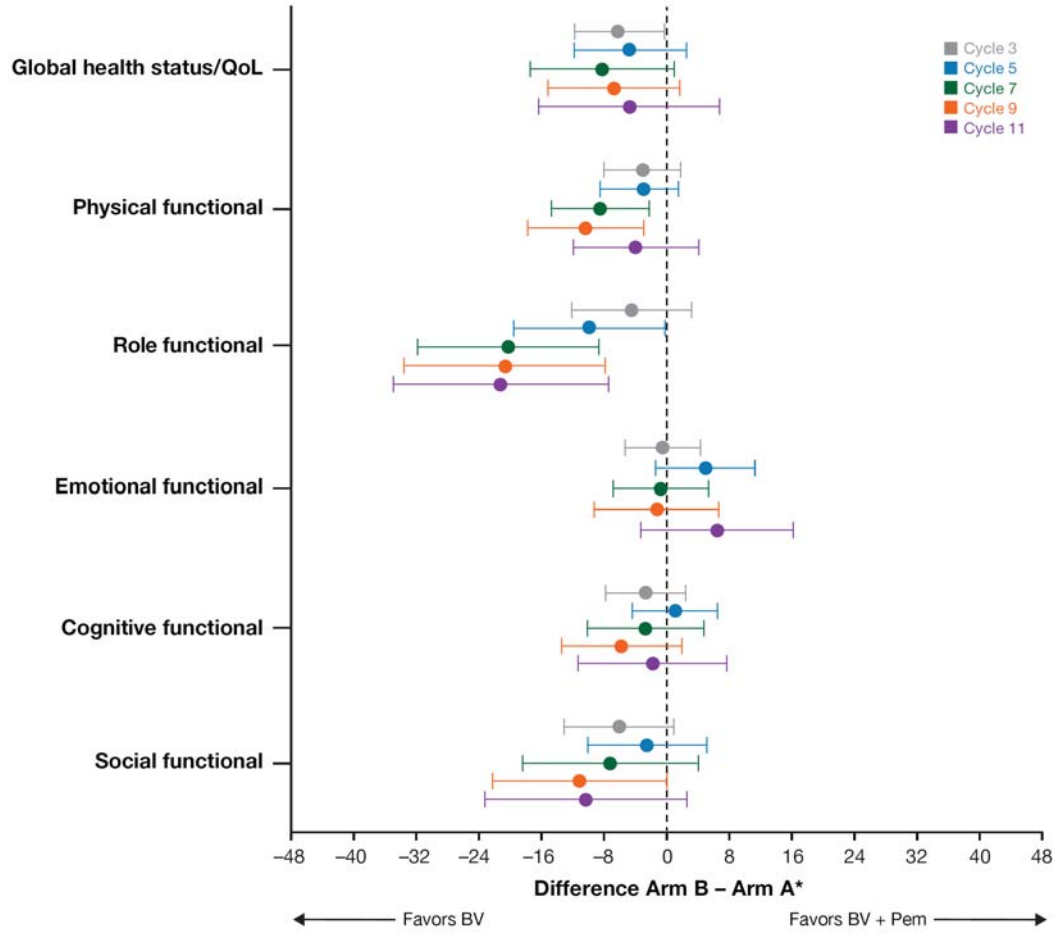


Figure 4. Forest Plot of the Differences Between Trial Arms in Changes of QLQ-C30 Global Health Status and Functional Domain Scores During Maintenance Cycles 3 through 11 Relative to Premaintenance Baseline Scores, Showing 95% Confidence Intervals.

Arm A, bevacizumab maintenance; Arm B, bevacizumab-plus-pemetrexed maintenance
BV, bevacizumab; EORTC, European Organization for Research and Treatment of Cancer; Pem, pemetrexed; QLQ-C30, Quality-of-Life Questionnaire–Cancer 30; QLQ-LC13, Quality-of-Life Questionnaire–Lung Cancer 13; QOL, quality of life.

QUALITY-OF-LIFE RESULTS (CONT.)	Of the 25 subscales measured in the EORTC QLQ-C30 and QLQ-LC13 questionnaires, 8 showed a clinically relevant change from pre-maintenance baseline in at least one maintenance cycle (Table 8). Of these, all except for pain in arm or shoulder favored the bevacizumab monotherapy arm. The majority of functional and symptom items in these questionnaires showed no statistically significant difference between treatment arms at more than one maintenance cycle. [Rittmeyer, 2011]
SAFETY RESULTS	Among patients randomized to maintenance treatment, grades 1, 2, 3, 4 and 5 AEs were reported in 92.2%, 84.5%, 45.6%, 7.3%, and 3.3% of patients, respectively, from induction to follow-up. Table 9 gives an overview of any-grade, grade ≥3, and SAE frequencies by time of occurrence (either during induction or maintenance or follow-up, or during the maintenance phase only) for the OS population (bevacizumab maintenance, bevacizumab-plus-pemetrexed maintenance, and no maintenance arms) and for patients randomized to each maintenance

arm. The table also lists the most commonly occurring AEs. Throughout the study, patients in the bevacizumab-plus-pemetrexed arm had a higher incidence of grade ≥3 AEs and SAEs than patients in the bevacizumab-alone arm.

The majority of toxicities were nonhematologic (Table 10). During maintenance, grade ≥3 hematologic toxicities occurred only in the bevacizumab-plus-pemetrexed group. Eleven (9.2%) and 22 patients (17.6%) in the bevacizumab and bevacizumab-plus-pemetrexed arms, respectively, discontinued bevacizumab because of an AE; 21 patients (45.7%) in the latter arm discontinued pemetrexed because of an AE.

Table 9. Summary of Adverse Events With Onset Any Time From Induction to Study End or During the Maintenance Phase.

	Safety Population		Bevacizumab (n=120)		Bevacizumab + Pemetrexed (n=125)	
Onset of Adverse Event	**Any Time (n=373)**	**MTC (n=245)**	**Any Time**	**MTC**	**Any Time**	**MTC**
Any-grade AEs (≥20%)						
Events, n	3674	1175	1170	402	1643	773
Patients with event, %	96.0	58.7	96.7	85.0	98.4	93.6
Grade ≥3 AEs						
Events, n	390	108	90	40	132	68
Patients with event, %	57.1	19.6	45.0	21.7	56.0	37.6
SAEs						
Events, n	217	48	34	16	70	32
Patients with event, %	37.0	10.2	21.7	13.3	33.6	17.6
Most common[a] any grade AEs (>20%)						
Patients with event, %	52.8	11.5	60.8	11.7	61.6	23.2
Nausea	32.7	13.1	36.7	18.3	44.0	21.6
Hypertension	27.1	7.2	35.8	8.3	25.6	13.6
Asthenia	23.6	5.1	27.5	2.5	26.4	12.8
Constipation	22.8	7.2	18.3	7.5	32.0	14.4
Fatigue	22.3	2.4	23.3	2.5	26.4	4.8
Vomiting	22.0	5.1	19.2	3.3	25.6	12.0
Decreased appetite	20.9	6.2	15.0	4.2	28.8	14.4
Diarrhea						
Most common[a] grade ≥3 AEs (>2%)						
Patients with event, %						
Neutropenia	8.8	1.9	10.0	0.0	9.6	5.6
Hypertension	8.0	2.4	6.7	2.5	16.0	4.8
Pulmonary embolism	4.0	0.8	2.5	1.7	1.6	0.8
Dyspnea	3.2	1.3	2.5	2.5	2.4	1.6
Anemia	2.9	1.1	0.8	0.0	4.0	3.2
Diarrhea	2.4	0.5	0.8	0.0	2.4	1.6
Fatigue	2.4	1.3	2.5	1.7	3.2	2.4
Hyperglycemia	2.4	0.8	1.7	0.8	2.4	1.6
Most common[a] SAEs (>1.5%)						
Patients with event, %						
Pulmonary embolism	3.8	0.8	2.5	1.7	1.6	0.8
Pneumonia	2.9	0.5	0.8	0.0	5.6	1.6
Neutropenia	1.9	0.0	0.0	0.0	0.0	0.0
Diarrhea	1.6	0.3	1.7	0.0	1.6	0.8
Renal failure	1.6	0.3	0.0	0.0	1.6	0.8

.[a]Events most commonly occurring at any on-study time (induction or maintenance or follow-up) in the overall safety population (bevacizumab maintenance, bevacizumab-plus-pemetrexed maintenance, and no maintenance arms).

AE, adverse event; MTC, maintenance phase; SAE, serious adverse event

Table 10. Summary of Hematologic and Nonhematologic Adverse Events With Onset Any Time From Induction to Study End or During the Maintenance Phase.

	Safety Population (n=373)		Bevacizumab (n=120)		Bevacizumab + Pemetrexed (n=125)	
Onset of Adverse Event	**Any time (n=373)**	**MTC[a] (n=245)**	**Any time**	**MTC**	**Any time**	**MTC**
Any-grade AE, n (%)[b]	123 (33.0)	31 (8.3)	43 (35.8)	8 (6.7)	45 (36.0)	23 (18.4)
Hematologic	217 (58.2)		116 (96.7)	102 (85.0)	122 (97.6)	115 (92.0)
Nonhematologic	356 (95.4)					
Grade ≥3 AE, n (%)[b]						
Hematologic	52 (13.9)	13 (3.5)	17 (14.2)	0 (0.0)	18 (14.4)	13 (10.4)
Nonhematologic	190 (50.9)	65 (17.4)	43 (35.8)	26 (21.7)	62 (49.6)	39 (31.2)
SAE, n (%)[b]						
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)

[a]Percentages calculated on the basis of the safety population (n=373). [b]Numbers of and percentages of patients experiencing the event are reported.

AE, adverse event; MTC, maintenance phase; SAE, serious adverse event.

SAFETY RESULTS (CONT.)

AEs of special interest

A total of 401 AEs of special interest occurred, with 58.2% (217/373) of patients in the safety population reporting an AE of special interest; 143 events occurred in 60.8% (73/120) of patients in the bevacizumab arm; 152 occurred in 67.2% (84/125) of patients in the bevacizumab-plus-pemetrexed arm; 106 occurred in 46.9% (60/128) of patients who did not receive maintenance treatment. The AEs of special interest that occurred at the highest frequency in the safety population at any on-study time were hypertension (experienced by 32.7%, 36.7%, 44.0%, and 18.0% of patients in the safety population, bevacizumab arm, bevacizumab-plus-pemetrexed arm, and patients not receiving maintenance treatment, respectively) epistaxis (18.0%, 21.7%, 19.2%, and 13.3%, respectively), and proteinuria (5.9%, 6.7%, 8.0%, and 3.1%, respectively).

Deaths

There were 153 (41.0%) deaths in the safety population, 41 (34.2%) deaths in the bevacizumab maintenance arm, 33 (26.4%) deaths in the bevacizumab-plus-pemetrexed arm, and 79 (61.7%) deaths in the group that did not receive maintenance treatment. Disease progression was the most frequent cause of death; 33.8%, 30.0%, 20.8%, and 50.0% of patients died as a result of disease progression in these respective groups. There were 10 (2.7%), 1 (0.8%), 1 (0.8%), and 8 (6.3%) deaths due to AEs with causal relationships to bevacizumab and/or pemetrexed in the safety population, bevacizumab arm, bevacizumab-plus-pemetrexed arm, and in patients not receiving maintenance treatment, respectively. There were no drug-related deaths during maintenance.

DSMB

An independent DSMB, including 1 biostatistician and 3 lung cancer specialists, was formed to review all safety data collected during the study. Three DSMB meetings were held, the first on April 29, 2010, the second on November 25, 2010, the third on March 30, 2011.

On behalf of DSMB, the chairmen signed off “certificates of non objection” to continue the study at each of the meetings.

At the first DSMB meeting details of the analyses required based on the preliminary safety data were discussed. Stopping rules were also

	discussed but ultimately not implemented.
SUMMARY	For patients of the all-patients population, the median duration of follow-up (including the induction phase) was 10.76 months for patients randomized to arm A and 11.07 months for patients randomized to arm B. The PFS duration was significantly higher in arm B compared with arm A (*P* value of unstratified log-rank test <.001; *P* value of stratified log-rank test <.001). The unstratified HR was below 1 with the upper 95% CI below 1, as well as the stratified HR, which was below 1 with the upper 95% CI below 1. The median PFS duration was 6.6 months in arm A while it was 10.2 months in arm B. The follow-up time was too short to observe enough survival events; therefore the OS data are immature. More SAEs were documented for patients treated in arm B (42 patients [33.6%]) compared with patients treated in arm A (26 patients [21.7%]). AEs with CTC-AE grade 3, 4, or 5 in any study phase have been recorded for more patients in arm B (70 patients [56.0%]) than for patients treated in arm A (54 patients [45.0%]). More patients died in arm A (41 patients [34.2%]) than in arm B (33 patients [26.4%]).
CONCLUSIONS	In the induction phase of AVAPERL, treatment with 4 cycles of bevacizumab plus cisplatin plus pemetrexed was associated with a high rate of disease control (71.9%). In the maintenance phase, bevacizumab plus pemetrexed provided significant improvements in PFS from induction, duration of response, and duration of disease control relative to bevacizumab alone.The median PFS value for patients in the bevacizumab-plus-pemetrexed arm of AVAPERL, 10.2 months from the start of induction, ranks among the highest recorded to date for patients with advanced NSCLC. It should be noted, however, that these patients represented a selected population in having achieved SD or PR after induction therapy. These data support the value of postinduction bevacizumab and indicate still more favorable effectiveness for continuation maintenance with the combination of bevacizumab and pemetrexed. The PFS advantage in the combination arm was evident irrespective of patient age, ECOG PS, smoking history, or response to induction (SD vs PR/CR). Although AVAPERL was not powered for OS and the number of OS events was small at the time of this analysis, data to date suggest a trend toward improved OS for patients in the bevacizumab-plus-pemetrexed arm. Limitations of the AVAPERL study include the lack of a pemetrexed monotherapy arm as a comparator, and the lack of re-baselined tumor assessments at the time of randomization. Toxicities observed in AVAPERL were as expected for these agents (eg, neutropenia, hypertension). No new or unexpected toxicities were observed. AEs irrespective of severity were more common during induction than during maintenance and were significantly more frequent in the bevacizumab-plus-pemetrexed maintenance arm. Results from AVAPERL, the first randomized phase III trial to compare maintenance bevacizumab with bevacizumab plus pemetrexed, support the use of the combination for patients with advanced NSCLC who can tolerate more intensive therapy. Additional trials that may further establish the efficacy and safety of bevacizumab-plus-pemetrexed maintenance (eg, ECOG 5508, PointBreak, NCT00948675) are ongoing or planned. These data, in composite, may prove instrumental in establishing optimal maintenance phase options to improve the standard of care for patients

	with advanced nonsquamous NSCLC.
REFERENCE	Rittmeyer A, Chouaid C, Kim J-H, et al: An analysis of health-related quality of life in patients with non-squamous non-small-cell lung cancer receiving bevacizumab versus bevacizumab plus pemetrexed for maintenance therapy in AVAPERL. The European Multidisciplinary Cancer Congress, Stockholm, Sweden, September 23–27, 2011 (poster 9076).
LIST OF APPENDICES	DSMB Certificates of non-objection DSMB Charter Protocol, version 1.0 Protocol, version 2.0 Protocol, version 3.0 SAP, inclusive addenda Statistical Report output tables and listings