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 (MO22089)

Achim Rittmeyer, MD, Vera Gorbunova, MD,† Anders Vikström, MD,‡ Arnaud Scherpereel, MD,§ Joo-Hang Kim, MD,‖ Myung-Ju Ahn, MD,¶ Antonio Chella, MD,# Christos Chouaid, MD,** Alicyn K. Campbell, MPH,†† and Fabrice Barlesi, MD, PhD‡‡*

Introduction: In the phase III AVAPERL trial, patients with advanced nonsquamous non–small-cell lung cancer receiving bevacizumab-plus-pemetrexed maintenance after first-line induction had a significant progression-free survival benefit relative to those treated with single-agent bevacizumab maintenance but with an increase in grade ≥3 adverse events. Here, we compare health-related quality of life (HRQOL) between AVAPERL maintenance arms.

Methods: Patient-reported outcomes were collected at designated intervals from preinduction to final visits. HRQOL was assessed using the self-administered European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 and the Quality of Life Lung Cancer–Specific Module 13. Differences in scores of 10 points or more between arms were above the minimum important difference threshold and considered clinically meaningful.

Results: During induction, patient-reported coughing symptoms improved slightly, whereas fatigue and appetite loss scores worsened relative to preinduction baseline. During maintenance, changes in mean global health status and the majority of Quality of Life Questionnaire Core 30 and Quality of Life Lung Cancer–Specific Module 13 subscale scores did not differ between trial arms by the minimum important difference defining clinically meaningful (better or worse) patient-reported outcomes. Exceptions were patient-reported role functional status, fatigue symptoms and appetite loss symptoms (favoring bevacizumab), and pain in arm or shoulder symptoms (favoring bevacizumab-plus-pemetrexed maintenance), which differed by clinically meaningful amounts at more than one maintenance assessment.

Conclusions: In AVAPERL, HRQOL remained relatively stable throughout maintenance and was generally similar in both arms. Despite an increase in adverse event rates, the addition of pemetrexed to bevacizumab maintenance resulted in similar stabilization of disease symptoms with improved efficacy outcomes.

Key Words: Patient-reported outcomes, Non–small-cell lung cancer, Bevacizumab, Pemetrexed, AVAPERL, Maintenance.

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*Department of Thoracic Oncology, Lungenfachklinik Immenhausen, Immenhausen, Germany; †N.N. Blokhin Cancer Research Center of Russia, Moscow, Russia; ‡Department of Pulmonary Medicine, Lungkliniken, Linköping, Sweden; §Pulmonary and Thoracic Oncology Department, Hôpital Albert Calmette, CHRU de Lille, Lille, France; ‖Department of Medical Oncology, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Korea; ¶Department of Hematology and Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; #Department of Cardio-Thoracic Medicine, University of Pisa, Pisa, Italy; **Service de Pneumologie, Assistance Publique - Hopitaux de Paris, Hôpital Saint-Antoine, Paris, France; ††Global Medical Affairs, Genentech, Inc., South San Francisco, California; and ‡‡Service d' Oncologie Multidisciplinaire & Innovations Thérapeutiques, Aix Marseille University, Assistance Publique Hopitaux de Marseille, INSERM CIC, Multidisciplinary Oncology and Therapeutic Innovations, Marseille, France.

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Address for correspondence: Achim Rittmeyer, MD, Lungenfachklinik Immenhausen, Robert-Koch-Strasse 3, DE-34376 Immenhausen, Germany. E-mail: arittmeyer@lungenfachklinik-immenhausen.de

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Although advances in first- and second-line treatments have improved survival outcomes in patients with stage IIIb or stage IV non–small-cell lung cancer (NSCLC), therapy remains palliative rather than curative.[1] Advanced NSCLC is associated with a significant burden from disease-related symptoms.[2–4] Improvement of disease symptoms, the effect of treatment-related adverse events, and health-related quality of life (HRQOL) are important factors when evaluating any treatment regimen in NSCLC and will only become more critical as improved treatment options further extend survival.[5,6]

Promising advances in NSCLC treatment include the targeting of specific genetic mutations present in some tumors, such as the *anaplastic lymphoma kinase* gene, as well as activating mutations of the epidermal growth factor receptor.[7,8] These are absent, however, in most patients who are likely agnostic for targetable mutations. In addition, obtaining

biopsy samples to determine mutational status is not always possible because of tumor location, and it remains far from clear whether a single biopsy taken from one tumor reflects the underlying genotype of that tumor or, by extension, of all tumors present.[9] For these reasons, improvements in systemic chemotherapy regimens remain essential to improving clinical outcomes for most patients with NSCLC.

Maintenance therapy following first-line induction is a broadly applicable approach to improve survival in advanced NSCLC. Continuation and switch maintenance therapies are potential strategies to augment the benefit of first-line therapy and are currently recommended as treatment options for patients with advanced NSCLC.[1,10,11] The anti–vascular endothelial growth factor monoclonal antibody bevacizumab and the antifolate agent pemetrexed have both proven to be important components in first-line induction regimens,[12–14] and accumulating evidence also supports their value in the maintenance setting. Phase III clinical trials have demonstrated the benefit of pemetrexed maintenance relative to placebo after platinum- or pemetrexed-based chemotherapy induction.[15,16] Recent meta-analyses[17,18] and exploratory analyses[19–21] have also associated maintenance treatment using bevacizumab with improved outcomes for patients with NSCLC.

Although continuation or switch maintenance appears to be important, few phase III trials have directly compared maintenance phase regimens.[22] One that did was the phase III AVAPERL (MO22089) trial, which compared bevacizumab plus pemetrexed with single-agent bevacizumab maintenance in patients with previously untreated advanced NSCLC who had achieved stable disease (SD) or partial response (PR) following four cycles of bevacizumab-cisplatin-pemetrexed induction. Combination maintenance therapy resulted in improved progression-free survival (PFS) compared with single-agent bevacizumab maintenance. The median PFS as measured from randomization was 7.4 versus 3.7 months (hazard ratio [HR] = 0.48 [95% confidence interval (CI), 0.35–0.66]; $p < 0.001$); as measured from induction, median PFS values were 10.2 versus 6.6 months (HR = 0.50 [95% CI, 0.37–0.69]; $p < 0.001$).[23] At a median follow-up time of 14.8 months, median overall survival from induction was numerically longer in the bevacizumab-plus-pemetrexed arm (19.8 versus 15.9 months (HR = 0.88 [95% CI, 0.64–1.22], $p = 0.32$).[24] Throughout the study, patients in the bevacizumab-plus-pemetrexed arm had a higher incidence of grade ≥3 adverse events and serious adverse events.[25] The most common grade ≥3 adverse events with onset in maintenance were hypertension and dyspnea (2.5% each) in the bevacizumab arm and neutropenia (5.6%), hypertension (4.8%), and anemia (3.2%) in the bevacizumab-plus-pemetrexed arm.

The observation of improved PFS, as well as an increase in adverse events associated with bevacizumab-plus-pemetrexed maintenance, underscores the importance of a comparative analysis of HRQOL in the maintenance arms of this study. Here we examine in detail the patient-reported HRQOL results from preinduction baseline through maintenance cycle 11, focusing on a comparison of changes in mean scores between trial arms for six patient-reported symptoms related to lung cancer treatment, five functional subscales, and global health status during maintenance.

MATERIALS AND METHODS

Eligibility and Treatment

Details of the AVAPERL study methodology and results were previously published.[23] Briefly, key inclusion criteria were documented stage IIIB or IV or recurrent NSCLC with one or more lesions measurable by Response Evaluation Criteria in Solid Tumors v1.1, as well as an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0, 1, or 2 at preinduction baseline. Patients with prior systemic treatment for lung cancer, a history of hemoptysis, or predominantly squamous cell histology were excluded. In the first part of the study, patients received induction therapy with bevacizumab (7.5 mg/kg intravenously [IV]), cisplatin (75 mg/m^2 IV), and pemetrexed (500 mg/m^2 IV) every 3 weeks (q3w) for four cycles. Throughout the trial, patients treated with pemetrexed received supplemental/prophylactic treatment with folic acid, vitamin B_{12}, and dexamethasone. Patients were assessed using Response Evaluation Criteria in Solid Tumors v1.1; those with complete response, PR, or SD after induction were eligible for the maintenance phase of the study. Follow-up continued for those with progressive disease. In the maintenance phase of AVAPERL, patients were randomized 1:1 to the bevacizumab monotherapy arm (7.5 mg/kg IV q3w) or the bevacizumab-plus-pemetrexed arm (bevacizumab, 7.5 mg/kg IV; pemetrexed, 500 mg/m^2 IV q3w). Maintenance treatment continued until one of the following: disease progression, unacceptable toxicity, withdrawal of consent, or death.

Patient-Reported Outcomes

The impact of disease- and treatment-related symptoms on HRQOL was assessed using the self-administered European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) questionnaire (QLQ-C30) version 3.0 and the associated EORTC Quality of Life Lung Cancer–Specific Module (EORTC QLQ-LC13).[26,27] Questionnaires were distributed and collected at preinduction baseline, prior to induction cycle 3 (week 6), at the postinduction response assessment (week 12), prior to maintenance cycle 1 (during weeks 11–13), every two cycles thereafter, at every follow-up visit, and at the final visit. Patients completed validated questionnaires in their local language. Questionnaires were scored based upon the EORTC scoring guidelines.[28] Mean scores for each of the QLQ-C30 and QLQ-LC13 subscales at each assessment from preinduction baseline to maintenance cycle 11 were calculated. Because of the small numbers of completed questionnaires available for later maintenance cycles (<40), these have not been included in the current analysis. For the maintenance phase of the study, changes in mean scores relative to premaintenance baseline for patients in each arm at maintenance cycles 3 through 11 were also calculated.

Included in the present analysis is the graphical presentation of mean scores for global health status, all five EORTC QLQ-C30 functional domains, and six symptom scales from the EORTC QLQ-C30 and QLQ-LC13 instruments, which include those considered most distressing by patients with lung cancer (e.g., cough, dyspnea, chest pain, appetite loss, and fatigue).[29,30] Data for other QLQ-C30 and QLQ-LC13 subscales are presented in Supplemental Table 1 (Supplemental Digital Content 1, http://links.lww.com/JTO/A462) and Supplemental Figures 1 (Supplemental Digital Content 2, http://links.lww.com/JTO/A463) and 2 (Supplemental Digital Content 3, http://links.lww.com/JTO/A464).

Statistical Methods

For the secondary trial end point of HRQOL, the objective was to detect and compare changes in EORTC QLQ-C30 and QLQ-LC13 subscale scores between the two treatment arms over the duration of the study. HRQOL analyses were based on an intent-to-treat (ITT) population, which was defined as all screened patients who were randomized to a maintenance arm. The frequency and percentage of missing data were calculated. The percentage of compliance was calculated as the number of completed assessments divided by the number of patients still on study in each arm at the measurement time point. Scores were only calculated if at least 50% of the items from the scale had been completed. Differences in any scores of ≥10 points were considered clinically meaningful.[31]

RESULTS

Patient and Disease Characteristics

A total of 414 patients were screened at 82 centers; 376 patients were enrolled, and 373 patients received induction. Some 253 patients were randomized to maintenance treatment. The ITT populations consisted of 125 patients in the bevacizumab arm and 128 patients in the bevacizumab-plus-pemetrexed arm. Patient and disease characteristics at preinduction baseline were similar for patients later randomized to both maintenance arms, with the exception of ECOG PS, for which a higher percentage of patients later randomized to bevacizumab-plus-pemetrexed maintenance had a score of 0 (52.4% versus 42.7%).[23] At premaintenance, baseline patient and disease characteristics, including ECOG PS (33.7% and 31.7% of patients having ECOG PS 0 in the bevacizumab-plus-pemetrexed and bevacizumab arms, respectively), were similar for both arms.

Questionnaire Completion Rates

Distribution and completion rates for the EORTC questionnaires are shown in Table 1. An imbalance in distribution rates was noted at all maintenance cycle time points, with questionnaires consistently being distributed at higher rates to patients randomized to the bevacizumab-plus-pemetrexed arm. Patients in both arms returned questionnaires at similar high rates (94.5%–100%).

Patient-Reported Induction and Maintenance Phase Outcomes

All QLQ-C30 and QLQ-LC13 subscales in which there were any clinically meaningful (≥10 point) changes from premaintenance baseline values in either trial arm during maintenance cycles 3 through 11 are listed in Table 2. Mean scores for global health and all QLQ-C30 functional scales from preinduction baseline through maintenance cycle 11 are shown in Figure 1. Mean subscale scores from the QLQ-C30 and the QLQ-LC13 questionnaires for six symptoms deemed to be most relevant for lung cancer patients from preinduction baseline through maintenance cycle 11 are shown in Figure 2.

Induction phase treatment was identical for patients who were later randomized to each of the treatment arms. However, there was a slight imbalance in global health and physical functional scores at premaintenance baseline, with mean scores for these scales being higher among patients randomized to the bevacizumab-plus-pemetrexed arm (Fig. 1). These differences, however, did not reach the minimum important difference. Over the course of induction therapy

TABLE 1. Compliance with Quality-of-Life Assessments in AVAPERL

	Bevacizumab			Bevacizumab + Pemetrexed		
	Patients on Study, No.	Distributed, No. (%)[a]	Completed, No. (%)[b]	Patients on Study, No.	Distributed, No. (%)[a]	Completed (%)[b]
Preinduction BL	125	121 (96.8)	118 (97.5)	128	126 (98.4)	121 (96.0)
Induction cycle 3	125	117 (93.6)	111 (94.9)	128	115 (89.8)	114 (99.1)
Premaintenance BL	120	119 (99.2)	119 (100)	125	125 (100)	124 (99.2)
Maintenance cycle 3	110	73 (66.4)	69 (94.5)	120	87 (72.5)	87 (100)
Maintenance cycle 5	83	52 (62.7)	50 (96.2)	98	81 (82.7)	77 (95.1)
Maintenance cycle 7	56	39 (69.6)	38 (97.4)	75	66 (88.0)	64 (97.0)
Maintenance cycle 9	48	33 (68.8)	33 (100)	59	52 (88.1)	50 (96.2)
Maintenance cycle 11	35	25 (71.4)	25 (100)	47	39 (83.0)	37 (94.9)

[a]Based on the number of on-study patients in the arm.
[b]Based on the number of questionnaires distributed.
BL, baseline.

TABLE 2. All EORTC QLQ-C30 and QLQ-LC13 Items Showing a Clinically Meaningful (≥10 point) Change from Premaintenance Baseline Values in Either Maintenance Arm

		MTC 3			MTC 5			MTC 7			MTC 9			MTC 11			
		BV	BV + P		BV	BV + P		BV	BV + P		BV	BV + P		BV	BV + P		
Questionnaire	**Item**	***N* = 69**	***N* = 87**	**Δ[a]**	***N* = 51**	***N* = 77**	**Δ[a]**	***N* = 38**	***N* = 64**	**Δ[a]**	***N* = 33**	***N* = 50**	**Δ[a]**	***N* = 25**	***N* = 37**	**Δ[a]**	**Favors**
QLQ-C30	Role functioning	5.9	1.3	−4.5	7.8	−1.9	−9.8	18.0	−2.3	**−20.3**	16.2	−4.7	**−20.8**	18.7	−2.7	**−21.4**	BV
	Fatigue symptoms	−7.0	−6.3	0.8	−6.1	−4.5	1.6	−11.0	−2.6	8.4	−12.8	−3.6	9.2	−8.9	−6.3	2.6	BV
	Nausea and vomiting symptoms	−9.1	−8.4	0.6	−10.1	−8.2	1.9	−14.5	−6.0	8.5	−20.2	−5.7	**14.5**	−14.7	−7.2	7.5	BV
	Appetite loss symptoms	−10.3	−6.1	4.2	−13.1	−3.9	9.2	−17.1	0.5	**17.6**	−20.8	0.0	**20.8**	−20.8	−2.7	**18.1**	BV
	Constipation symptoms	−7.4	−3.1	4.3	−10.5	1.7	**12.2**	−5.3	0.5	5.8	−5.1	2.7	7.7	−8.0	1.8	9.8	BV
QLQ-LC13	Pain in arm or shoulder symptoms	8.5	3.5	−5.0	8.2	−1.7	−9.9	0.0	−5.2	−5.2	9.7	−1.3	**−11.0**	12.5	0.0	**−12.5**	BV + P
	Alopecia symptoms	2.0	1.9	0.0	−3.5	1.3	4.8	−7.9	−1.0	6.9	−12.5	−8.7	3.8	−14.7	−10.8	3.9	BV
	Peripheral neuropathy symptoms	−0.5	4.7	5.2	4.1	9.5	5.4	4.5	12.0	7.5	−4.3	16.7	**21.0**	2.8	9.9	7.1	BV

Changes in mean scores relative to corresponding premaintenance baseline levels are shown. Bold font indicates a clinically meaningful difference between trial arms in change of mean scores relative to premaintenance baseline levels.

[a]Difference between trial arms (change in mean BV + P score relative to premaintenance baseline minus the change in BV score relative to premaintenance baseline).

BV, bevacizumab; EORTC, European Organisation for Research and Treatment of Cancer; MTC, maintenance cycle; P, pemetrexed; QLQ-C30, Quality of Life Questionnaire Core 30; QLQ-LC13, Quality of Life Lung Cancer–Specific Module.

cough decreased relative to preinduction baseline, indicating a slight improvement in patient status. On the other hand, patient-reported fatigue and appetite loss showed a trend toward worsening during induction (Fig. 2).

Patient-reported mean role functional and social functional scores were higher for patients in the bevacizumab arm at each maintenance cycle. However, in evaluating changes from premaintenance baseline values the differences between trial arms were clinically meaningful only for role functional scores at cycles 7, 9, and 11 (Table 2). Over the course of maintenance therapy mean scores for cough and pain in chest symptoms were stable and similar between arms, median patient-reported fatigue scores improved slightly in both arms, and dyspnea scores increased in the bevacizumab-plus-pemetrexed arm relative to premaintenance baseline. However, the differences between the trial arms in their respective changes from premaintenance baseline levels did not reach the clinical relevance threshold for any of these patient-reported outcomes (PROs; Table 2).

At four of the five maintenance phase assessments, mean scores for pain in arm or shoulder symptoms were higher in the bevacizumab arm, with clinically meaningful differences between arms in changes from premaintenance baseline levels favoring the bevacizumab-plus-pemetrexed arm at cycles 9 and 11. Mean appetite loss symptom scores decreased from premaintenance baseline levels by clinically meaningful amounts (range, 10.3–20.8 points) at all maintenance phase assessments among patients in the bevacizumab group, but it did not decrease from premaintenance baseline levels by a clinically meaningful amount (range, 6.1 to −0.5 points) at any maintenance assessment among patients treated with bevacizumab plus pemetrexed (Table 2); the difference in changes between trial arms favored the bevacizumab arm by clinically meaningful amounts at cycles 7, 9, and 11 (Table 2).

DISCUSSION

In the absence of curative therapy, HRQOL is a critically important aspect of any new treatment for advanced NSCLC. Although physician-reported adverse event collection is used to objectively evaluate disease- and symptom-related toxicities, only PROs reflect the symptom burdens and functional status changes as directly experienced by patients. As a result, HRQOL is increasingly incorporated as a secondary endpoint in NSCLC trials.[32–34] A real-world study of the importance to patients of symptom palliation—directly assessed via PROs—found that 68% of patients previously treated for advanced NSCLC with first-line platinum-based chemotherapy would choose chemotherapy, even with no survival benefit, over supportive care if it substantially reduced symptoms.[35,36] HRQOL for patients with NSCLC treated with maintenance phase bevacizumab or pemetrexed is now being investigated in a number of phase III trials, including AvaALL (MO22097),[37] PointBreak,[38] and ERACLE.[39]

In AVAPERL, induction phase therapy was associated with relatively stable functional scores. An initial imbalance

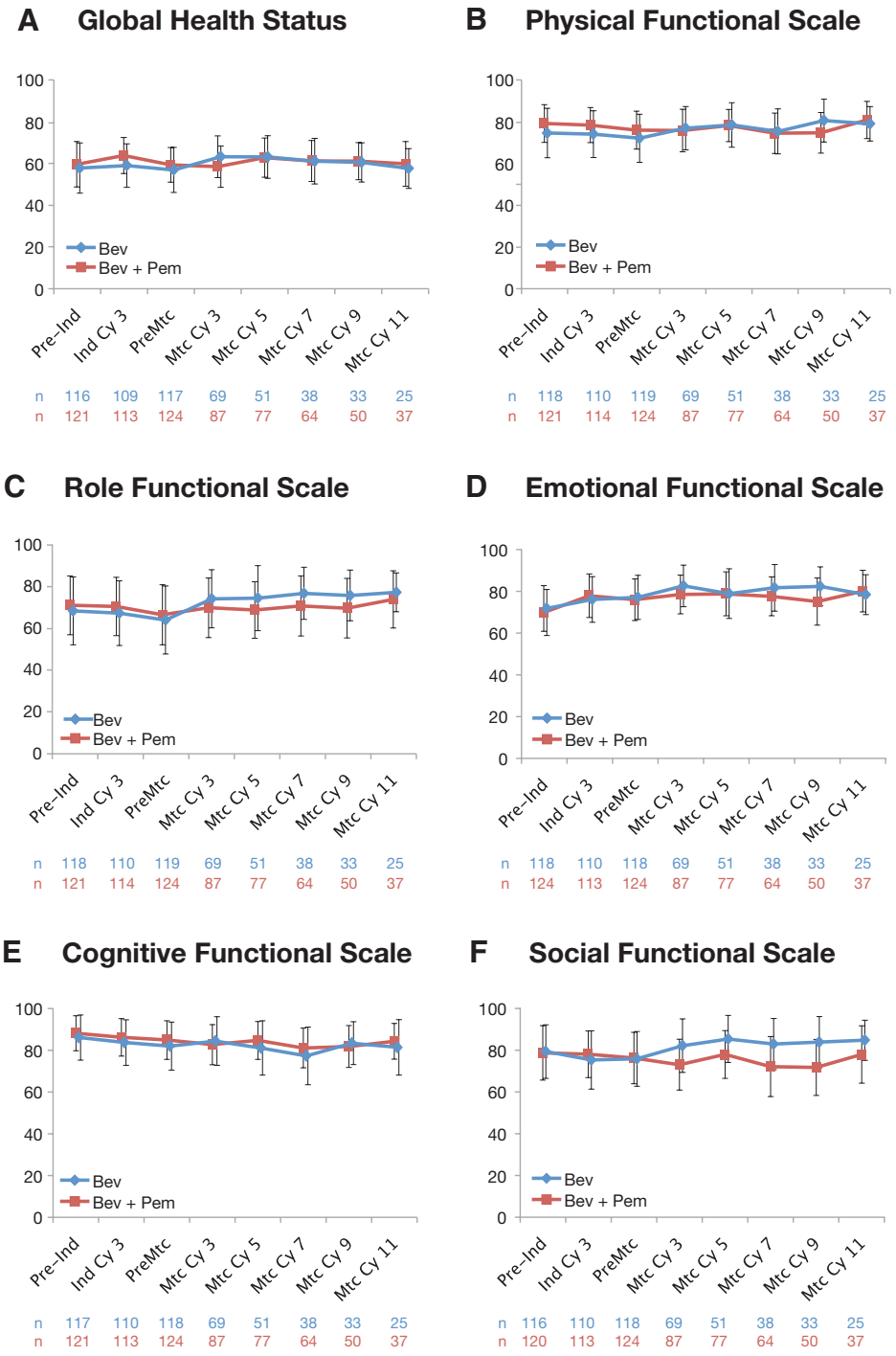

FIGURE 1. Mean scores, with standard deviations, for selected patient-reported European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) functional scales in AVAPERL, from preinduction baseline to maintenance cycle 11. Cy, cycle; Ind, induction; MTC, maintenance cycle; Preind, preinduction; PreMTC, premaintenance.

in ECOG PS at preinduction baseline may be reflected as a slightly higher mean physical functional score at preinduction and premaintenance baseline assessments. At premaintenance assessment, however, most scores, along with ECOG PS, were similar between arms. It is important to note that induction-phase PROs reported here were from patients achieving PR or standard deviation after induction therapy (a criterion for receiving maintenance therapy) and are not those of the entire ITT population at preinduction baseline.

During maintenance, mean scores for global health and most functional scales were similar in both arms, with largely overlapping standard deviation values. Role function and social function scores slightly favored the bevacizumab arm, and the symptoms scores for pain in arm or shoulder

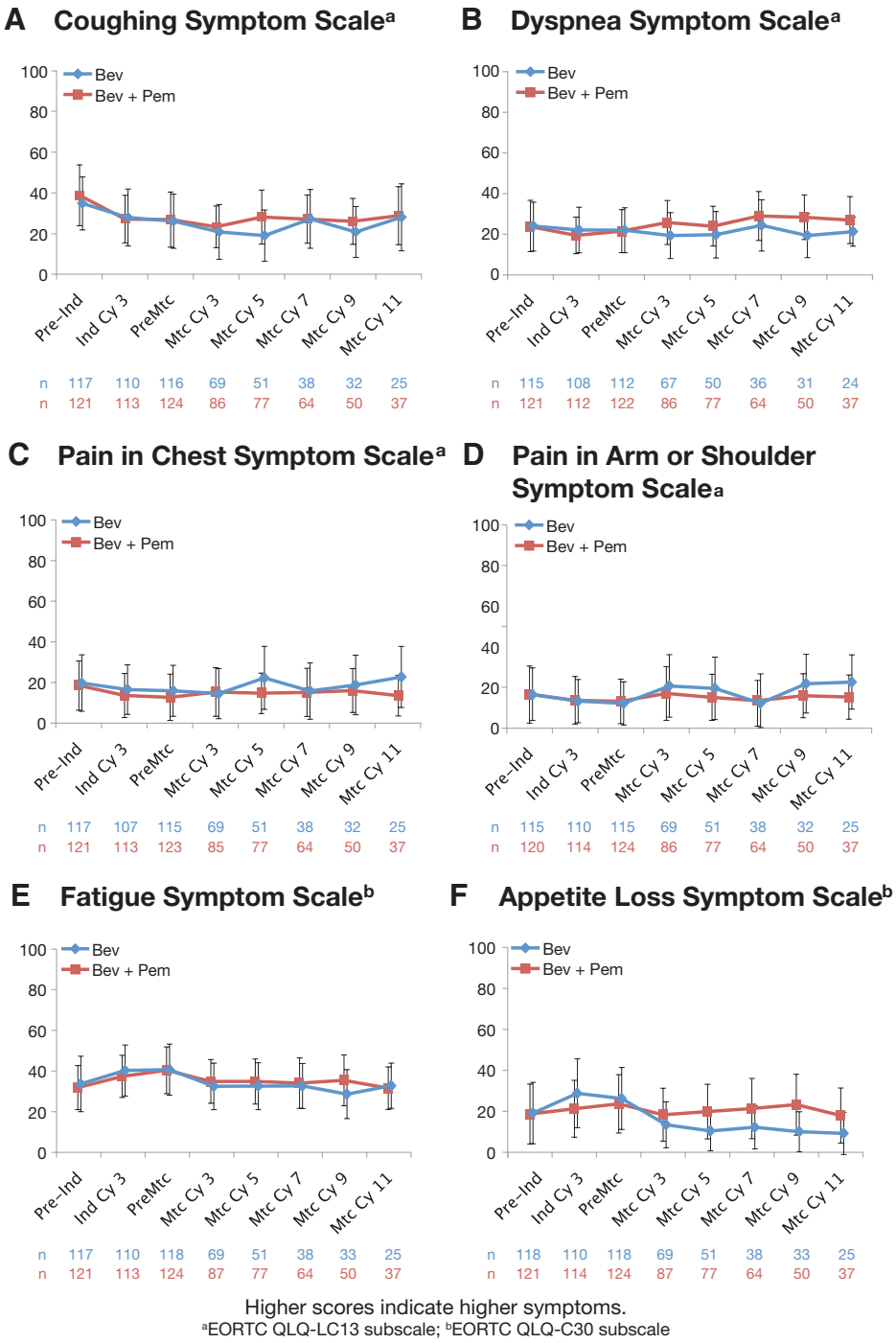

FIGURE 2. Mean scores, with SDs, for selected patient reported European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) and Quality of Life Lung Cancer–Specific Module (QLQ-LC13) symptom subscales in AVAPERL from preinduction baseline to maintenance cycle 11. Cy, cycle; Bev, bevacizumab; Ind, induction; MTC, maintenance cycle; Pem, pemetrexed; Preind, preinduction; PreMTC, premaintenance.

slightly favored the bevacizumab-plus-pemetrexed arm. Fatigue symptoms decreased after induction in both maintenance arms. The largest differences in symptom scores between arms were for appetite loss, with postinduction scores remaining stable for patients in the bevacizumab-plus-pemetrexed arm but decreasing noticeably for patients treated with bevacizumab alone. Similarly, patient-reported nausea/vomiting symptoms decreased relative to premaintenance levels in both maintenance arms, but improvements were more pronounced for patients in the bevacizumab-alone arm.

Limitations of this analysis include the consistently lower rate of compliance with HRQOL assessment in the bevacizumab-alone arm during maintenance treatment. These numbers seem to reflect lower questionnaire distribution rates rather than a reduced likelihood of patients in that arm completing the questionnaire. With this caveat in mind and despite the higher incidence of grade ≥3 adverse events

seen in the bevacizumab-plus-pemetrexed arm for the majority of subscales assessed, differences between trial arms were minor.[23,25] Thus, AVAPERL patients treated with bevacizumab plus pemetrexed received a clinical benefit in PFS from randomization (7.4 versus 3.7 months; HR = 0.48; $p < 0.001$) without reporting an adverse effect on HRQOL, while showing durability of disease symptom control, thereby supporting the value of this maintenance phase regimen as an important treatment option for patients with advanced or metastatic nonsquamous NSCLC.

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