Maintenance bevacizumab–pemetrexed after first-line cisplatin–pemetrexed–bevacizumab for advanced nonsquamous nonsmall-cell lung cancer: updated survival analysis of the AVAPERL (MO22089) randomized phase III trial


1Multidisciplinary Oncology and Therapeutic Innovations Department & Centre Investigation Clinique, Aix Marseille University, Assistance Publique Hôpitaux de Marseille, INSERM CIC, Marseille; 2Hôpital Calmette, CHRU de Lille, Lille, France; 3N.N. Blokhin Cancer Research Centre of Russia, Moscow, Russia; 4Centre François Baclesse, Caen, France; 5Lungkliniken, Linköping, Sweden; 6Assistance Publique-Hôpitaux de Paris, Hôpital Saint-Antoine, Paris, France; 7Department of Cardio-Thoracic Medicine, University of Pisa, Pisa, Italy; 8Yonsei Cancer Centre, Yonsei University College of Medicine, Seoul; 9Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; 10Hospital Grosshansdorf, Hamburg, Germany; 11Oncologia Medica, SS Annunziata, Sassari, Italy; 12National Cancer Center, Kyunggi-do, Korea; 13Department of Pulmonary Diseases, Amphia Hospital, Breda, and Erasmus MC Oncology Centre, Rotterdam, The Netherlands; 14Assistance-Publique-Hôpitaux de Marseille, Marseille, France; 15University Medical Center Groningen and University of Groningen, Groningen, The Netherlands; 16Lungenfachklinik Immenhausen, Immenhausen, Germany

Received 18 October 2013; revised 3 January 2014 and 12 February 2014; accepted 19 February 2014

Background: The randomized, phase III AVAPERL trial evaluated the safety and efficacy of bevacizumab maintenance with or without pemetrexed in nonsquamous nonsmall-cell lung cancer (nsNSCLC). Progression-free survival (PFS) was significantly prolonged with bevacizumab–pemetrexed, but overall survival (OS) data were immature. In this article, we report an independent, updated analysis of survival outcomes in AVAPERL.

Patients and methods: Patients with advanced nsNSCLC received first-line bevacizumab (7.5 mg/kg), cisplatin (75 mg/m²), and pemetrexed (500 mg/m²) every 3 weeks (q3w) for four cycles. Nonprogressing patients were randomized to maintenance bevacizumab (7.5 mg/kg) or bevacizumab–pemetrexed (500 mg/m²) q3w until progression or consent withdrawal. The primary end point of the trial was PFS; in this independent OS analysis, participating study centers were contacted to collect survival data on patients still alive at the time of the first analysis.

Results: A total of 376 patients received induction treatment. Disease control was confirmed in 71.9% of patients; 253 patients were randomized to maintenance treatment with bevacizumab (n = 125) or bevacizumab–pemetrexed (n = 128). At a median follow-up of 14.8 months, patients allocated to bevacizumab–pemetrexed had significantly improved...

*Correspondence to: Dr Fabrice Barlesi, Department of Multidisciplinary Oncology and Therapeutic Innovations, Aix Marseille University, Assistance Publique Hôpitaux de Marseille, 13915 Marseille Cedex 20, France. Tel: +33-4-91-96-59-01; Fax: +33-4-91-96-59-02; E-mail: fabrice.barlesi@ap-hm.fr

© The Author 2014. Published by Oxford University Press on behalf of the European Society for Medical Oncology.

All rights reserved. For permissions, please email: journals.permissions@oup.com.
PFS versus those on bevacizumab when measured from randomization [7.4 versus 3.7 months; hazard ratio (HR), 0.57, 95% confidence interval (CI) 0.44–0.75; P < 0.0001]. OS events occurred in 58% of all patients. OS was numerically longer with bevacizumab–pemetrexed versus bevacizumab when measured from randomization [17.1 versus 13.2 months; HR 0.87 (0.63–1.21); P = 0.29]. Second-line therapy was administered in 77% and 70% of patients in the bevacizumab and bevacizumab–pemetrexed arms, respectively. No new adverse events were reported during this updated analysis.

**Conclusion:** In an unselected population of nsNSCLC patients achieving disease control on platinum-based induction therapy, maintenance with bevacizumab–pemetrexed was associated with a nonsignificant increase in OS over bevacizumab alone.

**Key words:** nonsquamous, nonsmall-cell lung cancer, bevacizumab, pemetrexed, maintenance, chemotherapy

---

**introduction**

Prolonging overall survival (OS) remains a challenging goal in the treatment of advanced or metastatic nonsmall-cell lung cancer (NSCLC). First-line platinum doublet therapy that includes a taxane, gemcitabine, or vinorelbine, but no targeted agents, is associated with median survival times of 7–10 months and 1-year survival rates of 30%–40% [1, 2]. Patients with advanced nonsquamous NSCLC (nsNSCLC) derive benefit from the addition of bevacizumab, a humanized monoclonal antibody against vascular endothelial growth factor, to platinum-based regimens. When combined with first-line induction chemotherapy and continued as single-agent maintenance, bevacizumab has been shown to significantly prolong progression-free survival (PFS) compared with induction chemotherapy alone in two phase III trials of patients with advanced nsNSCLC [3–5]. In the Eastern Cooperative Oncology Group (ECOG) 4599 study, the use of bevacizumab with first-line paclitaxel–carboplatin also significantly extended OS relative to induction paclitaxel–carboplatin alone [median of 12.3 versus 10.3 months; hazard ratio (HR) 0.79; P = 0.003] [3]. Phase II clinical trials have also supported the use of bevacizumab in the maintenance setting, either as monotherapy or combined with pemetrexed, for patients with advanced nsNSCLC [6–8].

Pemetrexed is an effective antineoplastic agent when it is incorporated into platinum-based induction regimens, while reducing the occurrence of hematologic toxicity [9]. The use of pemetrexed as maintenance therapy has also been associated with survival benefits in randomized clinical studies of advanced nsNSCLC [10–12]. In patients with nonprogressive disease following cisplatin–pemetrexed induction, pemetrexed plus best supportive care (BSC) as maintenance treatment resulted in an improvement in OS versus BSC alone [median of 13.9 versus 11.0 months; HR 0.78; P = 0.020] [11]. A significant increase in OS was also observed with maintenance pemetrexed plus BSC when given after various platinum-based induction regimens in a separate trial compared with BSC alone [median of 15.5 versus 10.3 months; HR 0.70; P = 0.002] [12].

The randomized, phase III AVAPERL trial evaluated whether combination treatment with bevacizumab–pemetrexed in the maintenance setting would result in further improvements in efficacy over bevacizumab monotherapy in patients with advanced nsNSCLC whose disease had not progressed after first-line induction treatment with bevacizumab–cisplatin–pemetrexed [13]. Statistical significance in favor of maintenance bevacizumab–pemetrexed over bevacizumab alone was found for PFS, as measured from randomization (7.4 versus 3.7 months; HR 0.48; P < 0.001). At the time of analysis, however, median OS had only been reached in the maintenance bevacizumab-alone treatment arm (12.8 months from randomization). Given the unexpectedly large difference in PFS between treatment arms, the conduct of an updated survival analysis was deemed important. In this article, we report an independent analysis of updated PFS and OS outcomes in AVAPERL.

**patients and methods**

Full details of the patients and methods in AVAPERL (MO22089; NCT00961415) have been previously published [13]. This information is briefly summarized in the following sections.

**eligibility**

Eligible patients had previously untreated, inoperable, locally advanced (stage IIIb with supraclavicular lymph node or malignant pleural or pericardial effusion) [14], recurrent, or metastatic nsNSCLC (histologically or cytologically documented). Additional key eligibility criteria were ≥1 unidimensionally measurable lesion, an ECOG performance status (PS) of 0–2 at induction, and adequate organ function. Patients with predominantly squamous histology or a history of grade ≥2 hemoptysis were excluded. The protocol was approved by the institutional review boards and health authorities at the participating centers, and all patients provided informed consent. Patients from 82 centers in 11 countries were enrolled between August 2009 and July 2010.

**study design and treatment**

In this phase III, randomized, open-label study, patients received induction therapy consisting of bevacizumab (7.5 mg/kg i.v.), cisplatin (75 mg/m² i.v.), and pemetrexed (500 mg/m² i.v.) on day 1, every 3 weeks (q3w) for four cycles. Patients having a complete response (CR), partial response (PR), or stable disease (SD) after induction were randomized 1:1 to maintenance bevacizumab (7.5 mg/kg i.v.) or bevacizumab (7.5 mg/kg i.v.) plus pemetrexed (500 mg/m² i.v. with standard folic acid and vitamin B12 supplementation and dexamethasone prophylaxis) q3w. Randomization was stratified by sex, smoking status, and tumor response (SD versus PR) at randomization. Maintenance treatment was continued until progressive disease (PD), death, or consent withdrawal.

**survival update**

For this analysis, we contacted all participating centers to collect data regarding patients who were still alive at the time of the first analysis. The data collected were PFS from randomization, postprogression treatment(s), and date of death.
Efficacy analyses considered all randomized patients, whereas safety analyses were limited to patients who received at least one dose of any maintenance treatment.

The primary end point of AVAPERL was PFS from randomization until first PD or death from any cause. Secondary end points included OS from randomization to death from any cause, overall response rate (ORR), defined as the best (confirmed) response from the induction period, and quality of life. PFS and OS were compared between maintenance treatment arms using Kaplan–Meier estimates. HRs for PFS and OS were calculated using a stratified Cox regression model. Analyses related to the time from randomization to a PFS event or death were stratified by sex, smoking status, and induction response. Patients without a PFS or OS event were censored at the date of the last available tumor assessment at which they were known to be without progression, or the last survival update status. Univariate subgroup analyses evaluated time-to-event outcomes on the basis of age, ECOG PS, smoking history, and response to induction. Differences in response were analyzed using 95% Hauck–Anderson confidence intervals (CI) and a two-sided Cochran–Mantel–Haenszel $\chi^2$ test stratified by randomization variables. The study was powered to detect a statistical difference in PFS from the time of randomization, but it was not powered for OS.

results

patient disposition

A total of 376 patients were enrolled. Disease control following induction was confirmed in 71.9% (269 of 374) of patients with measurable disease at baseline (Figure 1). Of these, 253 patients were randomized to maintenance with bevacizumab ($n=125$) or bevacizumab–pemetrexed ($n=128$). Maintenance treatment was not administered to five patients in the bevacizumab arm and three patients in the bevacizumab–pemetrexed arm. At data cutoff, 140 patients (82 versus 58 in the bevacizumab and bevacizumab–pemetrexed arms, respectively) were treated to PD, 77 patients (29 versus 48) had discontinued intervention before PD, and 28 patients (9 versus 19) remained on maintenance treatment. Patient and disease characteristics were comparable between maintenance arms; briefly, 57% of patients were male, 47% had an ECOG PS of 0, 92% had stage IV disease, and 89% had adenocarcinoma histology [13].

study treatment

All patients randomized to maintenance therapy received four cycles of cisplatin during the induction phase. At the cutoff date for this extended analysis, nine patients in the bevacizumab arm and 19 in the bevacizumab + pemetrexed arm continued to receive maintenance treatment.

poststudy treatments

Postprogression treatment was administered to 92 patients (76.6%) in the bevacizumab arm and 88 (70.4%) in the bevacizumab–pemetrexed arm (Table 1). Second- and third-line postprogression therapies belonged mainly to the classes of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) and taxanes.

efficacy

At the time of this updated analysis, median follow-up time after randomization was 14.8 months (range 2.9–39.5 months). PFS events occurred in 116 (92.8%) patients in the bevacizumab arm and in 109 (85.2%) in the bevacizumab–pemetrexed arm. As in the primary analysis, patients allocated to maintenance with bevacizumab–pemetrexed had statistically significantly longer PFS compared with those allocated to single-agent bevacizumab (Figure 2).

OS events occurred in 73 (58.4%) and 74 (57.8%) patients in the bevacizumab monotherapy and bevacizumab–pemetrexed arms, respectively. Overall, 106 patients were censored, with 61 patients alive at the time of data cutoff. OS was numerically longer with bevacizumab–pemetrexed compared with bevacizumab when measured from induction [median of 19.8 versus 15.9 months; HR 0.88 (95% CI 0.64–1.22); $P=0.32$] and randomization [median of 17.1 versus 13.2 months; HR 0.87 (95% CI 0.63–1.21); $P=0.29$]; however, neither difference reached statistical significance between arms (Figure 3).

The 1-year OS rates were 67.7% (95% CI 59.3% to 76.1%) and 71.5% (95% CI 63.5% to 79.5%), and the 2-year OS rates were 34.1% (95% CI 24.7% to 43.5%) and 39.7% (95% CI 30.3% to 49.1%), for the bevacizumab-alone and bevacizumab–pemetrexed maintenance arms, respectively.

In univariate analyses, the PFS benefit with bevacizumab–pemetrexed was maintained across subgroups defined by age (<65 years; ≥65 years), ECOG PS (0 or 1 at baseline; 0, 1, or 2 at randomization), smoking history (never; current/past), and BORR to induction therapy (SD; PR/CR) (Figure 4). However, bevacizumab–pemetrexed was not shown to be associated with a statistically significant difference in OS (compared with bevacizumab) for any of these subgroups, as the 95% CIs crossed the 1.0 boundary for all evaluated subgroups.

safety and quality of life

Safety data have been reported previously [13]. Briefly, grade ≥3 adverse events (AEs) during maintenance therapy were observed in 26 (21.7%) and 47 (37.6%) patients in the bevacizumab and bevacizumab–pemetrexed arms, respectively. The most common grade ≥3 AEs for single-agent bevacizumab maintenance were hypertension (2.5%) and dyspnea (2.5%), and for bevacizumab–pemetrexed maintenance were neutropenia (5.6%), hypertension (4.8%), and anemia (3.2%). No new observed AEs were voluntarily reported by investigators during the collection of survival data. Full results of health-related quality-of-life measurements have been published elsewhere [15].

discussion

This extended analysis of the AVAPERL study corroborates our earlier finding that maintenance treatment with bevacizumab–pemetrexed significantly prolonged PFS relative to single-agent bevacizumab in patients with nsNSCLC who received induction bevacizumab–cisplatin–pemetrexed [13]. The AVAPERL study was not powered to detect differences in OS between treatment arms. The analysis revealed, however, that OS was numerically increased by nearly 4 months in patients treated with
maintenance bevacizumab–pemetrexed when compared with bevacizumab alone. This difference was apparent when survival was measured either from the start of induction or from randomization to maintenance, but it did not reach statistical significance. The use and type of postprogression therapy did not appear to contribute to potential differences in OS; in fact, a similar proportion of patients in the bevacizumab and bevacizumab–pemetrexed arms received a second-line (77% versus 70%, respectively) or third-line (38 versus 34%) therapy. The use of EGFR TKIs and other labeled therapies was equivalent in each treatment line.

The median duration of OS in the combination arm of AVAPERL is noteworthy because it exceeded 19 months from induction and 17 months from maintenance randomization. Although it must be acknowledged that there may be inaccuracies associated with cross-trial comparisons, and that such comparisons should be interpreted with caution, the median duration of OS with maintenance pemetrexed monotherapy...
Patients, n (%) | Bevacizumab (N = 120) | Bevacizumab + pemetrexed (N = 125)
---|---|---
Still receiving maintenance therapy | 9 (7.5) | 19 (15)
No postprogression treatment | 26 (22) | 19 (15)
Second-line therapy⁷ | N = 92 | N = 88
EGFR TKIs | 40 (43) | 47 (53)
Taxanes | 29 (32) | 16 (18)
Platinum-based therapy | 9 (10) | 10 (11)
Radiotherapy | 3 (3) | 8 (9)
Otherb | 11 (12) | 7 (8)
Third-line therapy⁷ | N = 45 | N = 42
EGFR TKIs | 11 (24) | 15 (36)
Taxanes | 14 (31) | 8 (19)
Platinum-based therapy | 4 (9) | 2 (5)
Radiotherapy | 6 (13) | 6 (14)
Otherb | 10 (22) | 11 (26)
Fourth-line therapy⁷ | N = 8 | N = 7
EGFR TKIs | 0 (0) | 1 (14)
Taxanes | 1 (13) | 1 (14)
Platinum-based therapy | 0 (0) | 2 (29)
Radiotherapy | 2 (25) | 1 (14)
Otherb | 5 (63) | 2 (29)

⁷Percentages are calculated using the total number of patients receiving second-, third-, or fourth-line therapy as the denominator. Some patients received combination of second-line treatments (mainly in clinical trials).

bIncluding pemetrexed. EGFR TKI, epidermal growth factor tyrosine kinase inhibitor.

from randomization has ranged from 13.9 to 15.5 months when evaluated in nonprogressing patients with nsNSCLC following platinum-based induction regimens in phase III trials [11, 12]. An exploratory analysis of the PointBreak study provides additional information on a potential benefit when combining bevacizumab and pemetrexed as maintenance therapy. In this phase III trial, patients with advanced nsNSCLC were randomized to induction pemetrexed–carboplatin–bevacizumab followed by maintenance bevacizumab–pemetrexed or to induction paclitaxel–carboplatin–bevacizumab followed by maintenance bevacizumab monotherapy [16]. OS in the intent-to-treat population, the primary end point, was similar between treatment arms (median of 12.6 versus 13.4 months, respectively; HR 1.00; \( P = 0.95 \)). However, the exploratory analysis among the patient subset treated with at least one cycle of maintenance therapy revealed numerically longer median OS from induction (17.7 versus 15.7 months) for those in the experimental arm receiving bevacizumab–pemetrexed rather than single-agent bevacizumab maintenance [17]. In another phase III trial (PRONOUNCE), nsNSCLC patients were randomized to receive pemetrexed plus carboplatin followed by maintenance pemetrexed or paclitaxel/carboplatin/bevacizumab followed by maintenance bevacizumab. OS in the intent-to-treat population, a secondary end point, was similar between treatment arms (median of 10.5 versus 11.7 months, respectively; HR 1.07; \( P = 0.615 \)) [18]. Because patients received different induction regimens in the PointBreak and the PRONOUNCE trials, it is not possible to make definitive conclusions about the relative benefit of maintenance treatment.

Results of the ongoing ECOG5508 study currently investigating different maintenance regimens containing bevacizumab, pemetrexed, or both, are awaited to help clarify the optimal approach for patients with advanced nsNSCLC [19]. Along with AVAPERL, this study is expected to provide important data to inform treatment decision making for the largest proportion of patients with NSCLC represented by those who have nonsquamous histology [20] and who lack genetic mutations associated with selection for other targeted agents [21, 22].

In conclusion, this analysis of the AVAPERL study demonstrated a statistically nonsignificant increase in OS of ~4 months with maintenance bevacizumab–pemetrexed when compared with single-agent bevacizumab in patients with advanced nsNSCLC and at least SD following bevacizumab–cisplatin–pemetrexed induction.

acknowledgements

We acknowledge Maria Luz Amador, Beatrix Lutiger, and Stefanie Srock, (F. Hoffmann-La Roche Ltd.) for their critical input on this manuscript. In addition, we thank Andrea Schulze (Parexel International, Berlin) for her contributions to the statistical analysis, and we acknowledge the contributions of the AVAPERL study investigators. France: Eric Pichon (Hôpital Bretonneau, Tours), Denis Moro-Sibilot (Hôpital Albert Michallon, Grenoble [La Tronche]), Lidia Petit (Hôpital Robert Debre, Reims), Michael Hummelsberger (Centre De Radiothérapie Onco Médicale, Beziers), Gael Deplanque, (Gh Paris Saint Joseph, Paris), Maurice Perol (Hôpital De La Croix Rousse, Lyon), Roland Schott (Centre Paul Strauss, Strasbourg), Rady Gervais (Centre Françoise Baclesse, Caen), Pierre-Jean Souquet (Centre Hospitalier Lyon-Sud, Pierre Bénite), Francoise Guichard (Polyclinique Bordeaux Nord Aquitaine, Bordeaux), Pierre Fournel (Hôpital Nord, Saint-Etienne), Pascal Thomas (CHI des Alpes du Sud Site de Gap, Gap), Jean Domas (Hôpital Saint Jean, Perpignan), Henri Janicot (Hôpital Gabriel Montpied, Clermont-Ferrand), Dominique Genet (Clinique Chenieux, Limoges), Gerard Zalcman (Hôpital Cote De Nacre, Caen), Henri Berard (HIA Sainte Anne, Toulouse), Isabelle Monnet (Centre Hospitalier Intercommunal, Creteil), Bénédicte Etienne-Mastroianni (Hôpital Louis Pradel, Bron), Lionel Falchero (Hôpital Nord Ouest, Gleize), Bernard Milleron (Hôpital Tenon, Paris), Christos Chouaid (Hôpital Saint Antoine, Paris), Germany: Frank Griesinger (Pius-Hospital, Oldenburg), Hubert Wirtz (Universitätsklinikum Leipzig, Leipzig), Yon-dschun Ko (Johanniter-Krankenhaus, Bonn), Corinna Eschbach (Asklepios Klinik Harburg, Hamburg), Elke Jaeger (Nordwest Klinik F., Frankfurt), Claus Steppert (Bezirksklinikum Obermain, Ebensfeld), Martin Reck (Krankenhaus Grosshansdorf, Grosshansdorf), Rudolf Huber (Ludwig-Maximilians Uni Klinik Innenstadt, Leipzig), Parvis Sadjadi (Johannes Wesling Klinikum Minden, Minden), Christian Grohé (Evang. Lungenklinik Berlin, Berlin), Bernhard Heinrich (Haematologisch–Onkologische Praxis; Dr Med Brudler, Heinrich, Bangerter, Muenchen), Joerg Mezger (St Vincentius
Figure 2. Kaplan–Meier estimates of PFS as measured from (A) induction treatment and (B) time of randomization, for patients allocated to maintenance therapy. CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.

Kliniken Ag, Karlsruhe), Claus-Peter Schneider (Zentralklinik Bad Berka Gmbh, Bad Berka), Wolfgang Schuette (Krankenhaus Martha-Maria, Halle), Cornelius Waller (Universitätsklinikum Freiburg, Freiburg); Greece: Marios Froudarakis (University Hospital of Alexandroupolis, Alexandroupolis); Italy: Antonio Chella (Azienda Ospedaliera Pisana–Ospedale Cisanello, Pisa), Alessandra Bearz (Centro Di Riferimento Oncologico, Aviano), Vincenzo Iaffaioli (Instituto Tumori Fondazione Pascale, Napoli), Oscar Alabiso (Ospedale Maggiore Della Carita, Novaro), Antonio Contu (Ospedale Civile, Sassari), Carlo Barone (Uni Cattolica Policlinico Gemelli, Roma), Vito Lorusso (Ospedale Vito Fazzi, Lecce), Adolfo Favaretto (Istituto Oncologico Venneto–A. O., Padova); Republic of Korea: Jin-Hyoung Kang (Kangnam St Mary’s Hospital, Seoul), Sang-We Kim (Asan Medical Center, Uni Ulsan College of Medicine, Seoul), Jong-Seok Lee (Bundang Seoul University Hospital, Bundang City), Hong Suk Song (Keimyung University Dongsan Medical Center, Daegu), Heung-Tae Kim (National Cancer Center, Kyunggi-do); Netherlands: B. Biesma (Jeroen Bosch Ziekenhuis, Jeroen Bosch), H.E. Codrington (Leyenburg Hospital, Den Haag), G.J.M. Herder (St Antonius
This work (NCT00961415) was supported by F. Hoffmann-La Roche, Ltd. Support for third-party writing assistance for this manuscript was provided by F. Hoffmann La-Roche, Ltd.
Figure 4. Univariate analyses of PFS and OS from time of randomization. Horizontal lines represent 95% CI. bev, bevacizumab; BORR, best overall response rate; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; OS, overall survival; pem, pemetrexed; PFS, progression-free survival; PR, partial response; PS, performance status; SD, stable disease.
F. Hoffmann-La Roche, Ltd provided an unrestricted grant for the updated survival analysis.

disclosure

The authors disclose the following potential conflicts of interest: FB has conducted research funded by F. Hoffmann-La Roche, Ltd and Eli Lilly, and has served on advisory boards for F. Hoffmann-La Roche, Ltd and Eli Lilly; AS has received research support from F. Hoffmann-La Roche, Ltd; AV has received honoraria, fees, and research support from F. Hoffmann-La Roche, Ltd; CC has received honoraria from and served on advisory boards for F. Hoffmann-La Roche, Ltd and Eli Lilly; HJMG has conducted research funded by F. Hoffmann-La Roche, Ltd, Eli Lilly, P. Boehringer Ingelheim; JGA has received research grants and honoraria from, and has served on advisory boards for F. Hoffmann-La Roche, Ltd and Eli Lilly; RJ has received fees for attending scientific meetings and speaking on behalf of AstraZeneca, Boehringer Ingelheim, GSK, Eli Lilly, Amgen, Pfizer, and F. Hoffmann-La Roche, Ltd; MR has received honoraria from and served on advisory boards for F. Hoffmann-La Roche, Ltd, Eli Lilly, Pfizer, BMS, AstraZeneca, and Boehringer Ingelheim; JGA has received research grants and honoraria from, and has served on advisory boards for F. Hoffmann-La Roche, Ltd and Eli Lilly; JGA has conducted research funded by F. Hoffmann-La Roche, Ltd, Eli Lilly, Boehringer Ingelheim, and Pfizer; VG, RG, AC, JHK, MJA, AP, HTK, CM, and AL have no conflicts to disclose.

references

17. Patel JD, Garon EB, Ramaswamy G et al. Exploratory analyses of efficacy and safety of pemetrexed (pem) plus bevacizumab (bev) and bev alone as maintenance therapy (MT) in patients (pts) with stage IIB or IV nonsquamous non-small cell lung cancer (NSCLC-MT). J Clin Oncol 2013; 31(suppl): 498s (Abstr 9012).
18. Zinner RG, Ross HJ, Weaver R et al. Randomized, open-label, phase III study of pemetrexed plus carboplatin (PemC) followed by maintenance pemetrexed versus placebo (PemC/PBC) followed by maintenance bevacizumab in patients with advanced nonsquamous (NS) non-small cell lung cancer (NSCLC). J Clin Oncol 2013; 31(suppl); abstr LB8003.
19. Dahlgberg SE, Ramalingam SS, Belani CP et al. A randomized phase III study of maintenance therapy with bevacizumab (B), pemetrexed (Pm), or a combination of bevacizumab and pemetrexed (Bp) following carboplatin, paclitaxel and bevacizumab (PCB) for advanced nonsquamous NSCLC: ECOG trial 5508 (NCT01107626). J Clin Oncol 2011; 29(suppl): 36s (Abstr TP5218).
21. Wong DW, Leung EL, So KK et al. The EML4-ALK fusion gene is involved in various histologic types of lung cancers from nonsmokers with wild-type EGFR and KRAS. Cancer 2009; 115: 1723–1733.