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


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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
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 therapy 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.
Haenszel χ2 and three patients in the bevacizumab before PD, and 28 patients (9 versus 19) remained on maintenance treatment. 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.

results
patient disposition
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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

Figure 1. Patient disposition.
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 paclitaxel 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.

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<td>Still receiving maintenance therapy</td>
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*aPercentages 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.
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.

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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.
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