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Isolating the Role of Bevacizumab in Elderly Patients With Previously Untreated Nonsquamous Non–Small Cell Lung Cancer

Secondary Analyses of the ECOG 4599 and PointBreak Trials

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Background: Patient-level data from 2 phase III studies in patients with previously untreated, advanced-stage, nonsquamous non–small cell lung cancer (NSCLC) were pooled to examine outcomes with bevacizumab and chemotherapy based on age.

Methods: Data from patients randomized to paclitaxel–carboplatin (PC) + bevacizumab in the Eastern Cooperative Oncology Group 4599 (E4599) and PointBreak studies were pooled and compared with E4599 patients randomized to PC alone. Patients were grouped by age: below 65, 65 to 74, 70 to 74, below 75, and 75 years or above. A multivariable model was used to calculate hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) using time-to-event outcomes. Adverse events (AEs) were assessed by age group in each study.

Results: The PC + bevacizumab and PC arms comprised 901 and 444 patients, respectively. PC + bevacizumab was associated with significant increases in overall survival relative to PC in patients below 65 years (hazards ratio [HR], 0.75; 95% confidence interval [CI], 0.62-0.89), 65 to 74 years (HR, 0.80; 95% CI, 0.68-1.00), 70 to 74 years (HR, 0.68; 95% CI, 0.48-0.96), and below 75 years (HR, 0.78; 95% CI, 0.68-0.89) but not in those aged 75 years or above (HR, 1.05; 95% CI, 0.70-1.57). Increased incidence of grade 3 to 5 AEs was reported with PC + bevacizumab versus PC in patients below 75 years (63% vs. 48%; P < 0.05) and 75 years or above (81% vs. 56%; P < 0.05) in E4599.

Conclusions: This analysis suggests that the survival benefits associated with PC + bevacizumab extend to patient subgroups below 75 years with advanced-stage NSCLC; no benefit, however, was observed for bevacizumab-eligible patients who were 75 years or above.

Key Words: bevacizumab, chemotherapy, elderly, non–small cell lung cancer


Non–small cell lung cancer (NSCLC) accounts for approximately 85% of lung cancer cases in the United States and poses a significant clinical challenge, as a majority of patients present with advanced-stage disease at diagnosis. Although first-line platinum-based chemotherapy has provided modest improvements in overall survival (OS) and progression-free survival (PFS) relative to other regimens, the prognosis for patients with advanced NSCLC remains poor, with 1-year survival rates of 30% to 40%.

Older patients are an important and sizeable subgroup within the NSCLC population; the median age at diagnosis is estimated to be 70 years. Although elderly patients are less likely to be eligible to participate in clinical trials, they may experience similar outcomes as younger patients when enrolled, particularly when treatment is chosen based on characteristics other than age.

Overexpression of vascular endothelial growth factor (VEGF-A), a key regulator of angiogenesis, occurs frequently in lung carcinomas. In the phase III Eastern Cooperative Oncology Group (ECOG) 4599 (E4599) study, the addition of bevacizumab, a humanized monoclonal antibody against VEGF-A, to paclitaxel–carboplatin (PC) significantly prolonged OS and PFS compared with PC alone in patients with NSCLC.

Controversy exists, however, as to whether elderly patients with NSCLC benefit from bevacizumab therapy to the same extent as younger patients. A post hoc analysis of study participants in E4599 found that patients 70 years or above who were treated with PC + bevacizumab had improved PFS, but not OS, compared with patients treated with PC alone. In addition, a significantly increased incidence of grade 3 to 5

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adverse events (AEs) was observed in patients in the PC + bevacizumab arm (87% vs. 61%, \( P < 0.001 \)). A retrospective analysis of the Surveillance, Epidemiology and End Results registry also found no improvement in survival for Medicare patients aged 65 years and above who received PC + bevacizumab versus PC alone for advanced NSCLC.16

In contrast, other recent analyses have supported the benefit of bevacizumab therapy in elderly patients with stage IIIB or IV NSCLC. The phase III AVAiL study,57 documented improved PFS for patients aged 65 years or above who received cisplatin–gemcitabine + bevacizumab 7.5 mg/kg versus cisplatin–gemcitabine alone, without an increase in the overall rate of grade ≥3 toxicities.18 The phase IV SAIL and ARIES observational studies documented similar rates of OS, PFS, and overall AEs among older and younger patient subsets treated with bevacizumab + chemotherapy, with the exception of lower survival rates in patients aged 80 years or above versus those below 80 years of age.19,20

To further examine the relationship between age and the efficacy and safety of bevacizumab therapy in patients with advanced NSCLC, we conducted a pooled analysis of patients receiving PC + bevacizumab in the E4599 and PointBreak trials.14,20

METHODS

Data Sources, Patients, and Treatment

This analysis was conducted using pooled individual patient data from the first-line, randomized, phase III E4599, and PointBreak studies. Information on the study designs and methodologies have been reported previously.14,20 Briefly, the E4599 trial (NCT00021060) randomized 878 patients with recurrent or advanced NSCLC to PC + bevacizumab or PC alone, with enrollment occurring between 2001 and 2004.15 In PointBreak (NCT00762034), 939 patients with stage IIIB or IV NSCLC were randomized to PC + bevacizumab or pemetrexed–carboplatin + bevacizumab from 2008 to 2012.20 The primary endpoint in both studies was OS.

Both trials employed similar treatment protocols and eligibility criteria; therefore, pooling the data for bevacizumab-treated patients across these 2 trials appeared appropriate. Two notable differences existed: patients with stable brain metastases were eligible for inclusion in PointBreak, whereas patients with brain metastases were excluded from E4599; in addition, induction therapy consisted of 4 cycles of PC + bevacizumab in PointBreak and 6 cycles in E4599. All patients provided signed informed consent to participate in each trial.

Statistical Analyses

Patient-level data were pooled from the PC + bevacizumab arms of the E4599 and PointBreak studies and compared with patients in the PC arm of the E4599 study. Analyses were based on data cutoff dates for E4599 of December 30, 2005, and for PointBreak of April 3, 2012. Patients were analyzed according to the following age subgroups: below 65 years, 65 to 74 years, 70 to 74 years, below 75 years, and 75 years or above. Age was measured continuously in days. In PointBreak, age subgroup analyses were prespecified, whereas age-based analyses were retrospective in E4599.14,20

The primary outcome of the analysis was OS (defined as the interval from randomization to death from any cause); secondary outcomes included PFS (defined as the interval from randomization to the earlier of progression or death from any cause), postprogression OS (defined as the time from first disease progression to death from any cause), best overall response rate (ORR), and toxicity. For time-to-event analyses, patients who had not experienced death or progression were censored at the most recent date they were known to be event-free. Responses for patients with measurable disease were assessed according to Response Evaluation Criteria in Solid Tumors, version 1.0.21 AEs were categorized using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 2 (E4599) or version 3 (PointBreak).

OS, PFS, and postprogression OS were calculated using Kaplan-Meier methods. An adjusted Cox proportional hazards model was used to estimate hazard ratios (HRs) and confidence intervals (CIs) for survival outcomes in the pooled PC + bevacizumab population from both trials compared with the PC-alone arm in E4599, adjusting for sex, race, histology, disease stage, and ECOG performance status. The Fisher exact tests were used to compare ORR and the incidence of AEs between groups. Statistical analyses were performed using SAS 9.2 software (SAS Institute Inc., Cary, NC), and a \( P \)-value of <0.05 was considered statistically significant.

The primary analysis compared clinical outcomes with PC + bevacizumab to PC alone within age subgroups using pooled data from E4599 and PointBreak. Because of differences in event reporting and data availability between the 2 studies, analyses of treatment exposure, protocol deviations, and postprogression OS were conducted only for patients enrolled in E4599, as pooling these data was not possible. AEs were reported separately for each study.

RESULTS

Patient Characteristics

A total of 434 and 467 patients were randomized to PC + bevacizumab in the E4599 and PointBreak trials, respectively. In the pooled PC + bevacizumab population, 485 (53.3%) patients were below 65 years, 302 (33.5%) were 65 to 74 years, 130 (14.4%) were 70 to 74 years, 787 (87.3%) were below 75 years, and 114 (12.7%) were 75 years or above. A total of 444 patients in E4599 received PC alone, of whom 250 (53.6%) were below 65 years, 151 (34.0%) were 65 to 74 years, 73 (16.4%) were 70 to 74 years, 401 (90.3%) were below 75 years, and 43 (9.7%) were 75 years or above. Baseline characteristics were generally similar between the age subgroups (data not shown) and between the pooled population and the PC arm in elderly patients, although the PC arm included a higher proportion of males and a lower proportion of adenocarcinoma histology than the PC + bevacizumab arm among patients below 75 years (Table 1 and see Supplemental Digital Content, http://links.lww.com/AJCO/A77).

Efficacy

The use of bevacizumab was associated with a significant reduction in the risk of death for patients aged below 65 years (hazards ratio [HR], 0.75; 95% confidence interval [CI], 0.62-0.89), 65 to 74 years (HR, 0.80; 95% CI, 0.64-1.00), 70 to 74 years (HR, 0.68; 95% CI, 0.48-0.96), and below 75 years (HR, 0.78; 95% CI, 0.68-0.89) in the pooled population (Fig. 1A). Among the 157 patients aged 75 years or above, the difference in OS was not statistically significant between treatment arms (HR, 1.05; 95% CI, 0.70-1.57). A similar pattern of OS benefit with PC + bevacizumab compared with PC alone was seen across age subgroups when comparing outcomes exclusively in the E4599 trial (Fig. 1B). The unadjusted Kaplan-Meier estimates for OS in the pooled analysis are shown for patients aged below 75 years and 75 years or above in Figure 2.

With respect to PFS, treatment with PC + bevacizumab in the pooled population was associated with a significant reduction in the risk of progression or death compared with PC
Survival among patients aged 75 years or above was a nonsignificant trend in favor of the PC arm for postprogression OS (median: 5.0 mo for PC + bevacizumab vs. 6.6 mo for PC; HR, 1.30; 95% CI, 0.77-2.30).

Safety

In the E4599 study, the overall incidence of grade ≥3 AEs was significantly higher in the PC + bevacizumab arm than in the PC arm (Table 2) and proportionately greater in those aged 75 years or above: 63% for PC + bevacizumab versus 48% for PC in patients below 75 years (P < 0.05) and 81% versus 56%, respectively, in patients aged 75 years or above (P < 0.05). Statistically significant increases in the rate of grade ≥3 neutropenia, hypertension, hemorrhage, proteinuria, and thromboembolism were reported with PC + bevacizumab relative to PC in patients below 75 years. Grade 5 AEs were increased in the PC + bevacizumab arm; the relative incidence in patients aged 75 years or above receiving PC + bevacizumab versus PC alone was 8% (5/59) and 2% (1/43), respectively (P = 0.192). In the subgroup of patients below 75 years, grade 5 AEs occurred in 17 patients (5%) in the PC + bevacizumab arm compared with only 1 patient (0.2%) in the PC arm.

In the PointBreak trial, the incidence of grade ≥3 AEs with PC + bevacizumab was 65% in patients aged below 75 years and 77% in patients aged 75 years or above. The incidence of grade 5 AEs was 2% for both the below 75 and 75 years or above age groups (Table 2).

Patients receiving PC + bevacizumab were more likely to discontinue treatment because of an AE than those receiving PC (17% [65/375] and 12% [49/401] of patients aged below 75 years and randomized to PC + bevacizumab and PC alone, respectively). In contrast, treatment discontinuation rates in the same arms were 29% (17/59) and 19% (8/43), respectively, in patients aged 75 years or above.

DISCUSSION

In this exploratory analysis, patient data from the phase III E4599 and PointBreak studies were pooled to further evaluate the benefits and risks of bevacizumab therapy in patients with advanced NSCLC based on age. The age cohorts used were designed to provide subgroups of sufficient size to draw clinically meaningful conclusions regarding outcomes in relevant elderly populations. The analysis confirmed significant improvements in OS and PFS with the addition of bevacizumab to PC for patients aged below 65, 65 to 74, 70 to 74, and below 75 years. There was no significant benefit in survival observed with the use of bevacizumab in patients aged 75 years or above, although the relatively small number of
patients in this subgroup (n = 157) limited the statistical power of the analyses conducted in this population. Pooling data from patients who received PC + bevacizumab in 2 phase III trials enhanced the statistical power of these analyses and distinguished the results from previously conducted analyses. Specifically, Ramalingam et al.\textsuperscript{15} observed no statistically significant benefit from bevacizumab in patients aged 70 years or above in the E4599 trial, whereas the results described here demonstrate that benefit was extended to patients aged 70 to 74 years. This subgroup represents a significant population of

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**FIGURE 1.** Forest plots of overall survival (OS) (A and B) and progression-free survival (PFS) (C and D) for patients treated with paclitaxel–carboplatin + bevacizumab versus paclitaxel–carboplatin alone, by age subgroup. CI indicates confidence interval; HR, hazard ratio.
Safety analyses in E4599 patients showed that treatment with PC + bevacizumab was associated with a significantly higher incidence of overall grade ≥ 3 AEs compared with PC alone in patients below 75 years old and in those aged 75 years or above. The incidence of grade 5 events in patients aged 75 years or above was 8% for those receiving bevacizumab with PC compared with 2% for those receiving chemotherapy alone, although the difference did not reach statistical significance. Grade 5 AEs occurred in 2% of patients who were 75 years of age or above in the PointBreak study. These results are in line with previous reports that indicated a higher likelihood of developing grade ≥ 3 AEs for older patients receiving bevacizumab with chemotherapy.15,22

It is worth considering these results in the context of other recent reports that describe outcomes in elderly NSCLC patients treated with bevacizumab + chemotherapy in clinical trials.15,18,19 In a previous E4599 post hoc analysis, which found no OS benefit with bevacizumab + chemotherapy in patients aged below 75 years and above 75 years, the age cutoff was 70 years or above.15 Conversely, other analyses that have supported the risk:benefit of bevacizumab in both younger and older patients used 65 years, the age at which individuals are eligible for Medicare in the United States, as the age cutoff.18,19

Together with the current analysis, these findings suggest that the population-level benefit of bevacizumab + chemotherapy in NSCLC is less consistent with advancing age and that 75 years of age may be a more practical delineation of “elderly” than 65 or 70 years of age, particularly as the average age of patients diagnosed with NSCLC continues to rise.

The reasons for the lack of observed clinical benefit with bevacizumab + chemotherapy in patients above 75 years in this analysis are likely wide-ranging. For instance, age-related decreases in renal function, immune response, and bone marrow regeneration may impact tolerance and response to therapy.23 The presence of comorbidities, such as respiratory or cardiovascular disorders, may also influence clinical outcomes and can exacerbate treatment-related toxicities, ultimately leading to decreased treatment duration in older patients.24–27 Potentially confounding these findings are the longer-than-expected median OS durations observed in the control arm of E4599 (13.0 mo) and the observed nonsignificant decrease in postprogression OS with PC + bevacizumab in the older patient subgroup, which may have contributed to the apparent lack of clinical benefit with bevacizumab in those above 75 years of age.

Despite these concerns, it is increasingly clear that elderly patients, when properly selected, can benefit from standard cancer therapies. Although elderly patients are less likely than younger patients to receive chemotherapy for advanced NSCLC,24–26 retrospective and prospective analyses from phase III trials have shown that platinum-doublet chemotherapy is associated with greater survival benefits than single-agent therapy in elderly populations and that modern third-generation platinum-based combinations are superior to older combinations.25–29 Increasing evidence also suggests that performance status and comorbidities, rather than age, are

![Graph A](image1)

**FIGURE 2.** The Kaplan-Meier estimates for overall survival in patients treated with paclitaxel–carboplatin + bevacizumab (pooled population) versus paclitaxel–carboplatin alone: (A) patients aged below 75 years and (B) patients aged 75 years or above. CI indicates confidence interval; HR, hazard ratio; PC, paclitaxel plus carboplatin.
more appropriate factors to determine which patients should undergo intensive therapy. 7,22

Limitations of the current analysis include its exploratory, post hoc nature, the limited size of the patient population aged 75 years or above, and the lack of adjustment for unmeasured potential confounding factors (eg, comorbidities). As is the case with all post hoc exploratory analyses, we cannot definitively conclude a treatment benefit, or lack thereof, based on these subgroup analyses. We also note that PointBreak did not include a non-bevacizumab control group. However, the consistency of the results observed in the pooled analysis and in the E4599 study alone shown in Figure 1 suggests that the use of the control arm of E4599 as a comparator did not bias the results of the pooled analysis. In addition, differences in reporting between the E4599 and PointBreak studies did not allow for the pooling of data on treatment exposure, post-progression survival, or safety. However, eligibility for the 2 studies was virtually identical, and the difference in intended treatment duration during induction (6 cycles in E4599 vs. 4 cycles in PointBreak) was deemed unlikely to have much bearing on final outcomes.

We also recognize that older patients who participate in clinical trials represent those on the healthier end of the spectrum and may be very different from the general population of older patients with advanced NSCLC. In fact, a greater percentage of patients included in this analysis aged 75 years or above had an ECOG performance status of 1 compared with younger patient subgroups. Performance status and comorbidities should be taken into consideration, along with age, when determining treatment for patients.

In conclusion, this pooled analysis suggests that younger segments of the elderly population (ie, those between the ages of 65 and 75 years) with advanced NSCLC appear to derive meaningful clinical benefit from the addition of bevacizumab to standard PC chemotherapy. Similar benefits were not observed in patients with NSCLC above 75 years of age. Improving outcomes for patients above 75 years remains an important research priority.

REFERENCES


