Carboplatin and Paclitaxel With vs Without Bevacizumab in Older Patients With Advanced Non–Small Cell Lung Cancer

Junya Zhu, MS, MA
Dhruv B. Sharma, PhD
Stacy W. Gray, MD, AM
Aileen B. Chen, MD, MPP
Jane C. Weeks, MD, MS
Deborah Schrag, MD, MPH

Non–small cell lung cancer (NSCLC) is usually diagnosed at advanced stage (IIIB or IV), when cure is rarely attainable. Although chemotherapy offers modest quality-of-life and survival advantages over best supportive care, treatment outcomes remain disappointing, with 1-year survival less than 50% and 3-year survival less than 25%.

Bevacizumab inhibits tumor angiogenesis and subsequent tumor growth and metastases. In 2006, a randomized trial conducted by the Eastern Cooperative Oncology Group (ECOG 4599) of 878 patients with advanced NSCLC of non–squamous cell type demonstrated a significant survival benefit for bevacizumab–carboplatin–paclitaxel therapy compared with carboplatin–paclitaxel therapy alone. One-year survival probabilities were 39.6% (95% CI, 34.6%-44.5%) for bevacizumab–carboplatin–paclitaxel vs 40.1% (95% CI, 37.4%-43.0%) for carboplatin–paclitaxel in 2002-2005. Neither multivariable nor propensity score–adjusted Cox models demonstrated a survival advantage for bevacizumab–carboplatin–paclitaxel compared with carboplatin–paclitaxel cohorts. In propensity score–stratified models, the hazard ratio for overall survival for bevacizumab–carboplatin–paclitaxel compared with carboplatin–paclitaxel in 2006-2007 was 1.01 (95% CI, 0.89-1.16; P = .85) and compared with carboplatin–paclitaxel in 2002-2005 was 0.93 (95% CI, 0.83-1.06; P = .28). The propensity score–weighted model and propensity score–matching model similarly failed to demonstrate a statistically significant superiority for bevacizumab–carboplatin–paclitaxel. Subgroup and sensitivity analyses for key variables did not change these findings.

Conclusion Adding bevacizumab to carboplatin and paclitaxel chemotherapy was not associated with better survival among Medicare patients with advanced NSCLC.

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1-year overall survival when adding bevacizumab to standard chemotherapy. Moreover, the ECOG trial failed to demonstrate a survival advantage for bevacizumab-carboplatin-paclitaxel over carboplatin-paclitaxel (HR, 0.89; 95% CI, 0.70-1.14) among the subgroup of 366 trial participants aged 65 years or older. An unplanned subset analysis in 224 patients aged 70 years or older at diagnosis from the same trial also suggested no significant differences in overall survival (11.3 vs 12.1 months) between bevacizumab-carboplatin-paclitaxel and carboplatin-paclitaxel. Notwithstanding the uncertainty about benefits in the population aged 65 years or older, the Centers for Medicare & Medicaid Services (CMS) has covered bevacizumab therapy for its enrollees subsequent to FDA approval. Little is known about how clinicians have interpreted efficacy studies to formulate treatment recommendations, and given that approximately two-thirds of patients with lung cancer receive their diagnoses at age 65 years or older, establishing the survival advantage of bevacizumab in the Medicare population is a priority for informed decision making.

Using analytic strategies to address confounding and selection bias caused by the lack of treatment randomization in observational studies that may limit ability to make valid inferences about causality, we examined whether bevacizumab-paclitaxel and carboplatin-paclitaxel were associated with improved survival in the Medicare population with advanced non–small cell NSCLC.

METHODS

Data Source

We used population-based data from the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) program linked to Medicare claims. The SEER database covers 17 cancer registries and captures cancer incidence for approximately 28% of the US population. SEER includes information on cancer site, histology, stage, grade, and dates of diagnosis and death, as well as patient demographic characteristics. Medicare Parts A and B claims contain extensive service-level data for hospital inpatient and outpatient, skilled nursing facility, home health agency, and hospice care, as well as physician services and durable medical equipment. SEER data for patients with diagnoses from January 1, 2002, through December 31, 2007, were matched to Medicare claims data from January 1, 2001, through December 31, 2009. The study was approved by the institutional review board at the Dana-Farber Harvard Cancer Center.

Study Participants

The study cohort included patients aged 65 years or older with pathologically confirmed stage IIIB or IV non–small cell NSCLC diagnosed between 2002 and 2007 who received first-line chemotherapy with bevacizumab-carboplatin-paclitaxel or carboplatin-paclitaxel within 4 months of diagnosis. Patients were excluded if they had other primary cancers diagnosed either before or after NSCLC or died within 30 days of NSCLC diagnosis. To ensure completeness of Medicare claims information, patients who were not continuously eligible for Medicare Parts A and B or who were enrolled in a health maintenance organization at any point from diagnosis to death or 6-month follow-up were also excluded. Staging information was available in SEER and defined according to the American Joint Committee on Cancer (AJCC) staging manual, 6th edition.

The goal of this analysis was to compare survival outcomes for elderly patients with advanced NSCLC who received first-line carboplatin and paclitaxel alone with those who also received bevacizumab. Thus, our primary comparison groups were patients with diagnoses in 2006-2007 receiving first-line bevacizumab-carboplatin-paclitaxel and those with diagnoses in 2006-2007 receiving first-line carboplatin-paclitaxel. We also constructed a second control group composed of patients with diagnoses in 2002-2005 before bevacizumab was commercially available. The carboplatin-paclitaxel 2002-2005 group was used to mitigate bias caused by selecting patients into either treatment or control group based on patients’ characteristics that might also be associated with outcomes. If, in 2006 and 2007, physicians chose bevacizumab-carboplatin-paclitaxel for their healthier patients, then a selection bias might result in better survival for those patients. Between 2002 and 2005, bevacizumab was not available, so comparing the carboplatin-paclitaxel 2002-2005 cohort with the bevacizumab-carboplatin-paclitaxel cohort would attenuate this potential bias. At the minimum follow-up observation time of 24 months after diagnosis, 83% of cohort members were deceased.

Identification of First-line Carboplatin, Paclitaxel, and Bevacizumab

Medicare claims have been shown to have high sensitivity and specificity for identification of chemotherapy agents among elderly patients with lung cancer. First-line chemotherapy was defined as chemotherapy administered within 4 months after the NSCLC diagnosis. Specific agents were identified from Medicare outpatient, physician, or durable medical equipment claims by using Healthcare Common Procedure Coding System codes and National Drug Codes. The date of the first chemotherapy claim was considered the start date of chemotherapy. Additional agents received within 8 days of the first drug were considered components of the same regimen. Any patients whose initial chemotherapy was delivered concurrently with radiotherapy, defined as start dates within 8 days of each other, were excluded.

Survival Outcomes

The primary outcome was all-cause mortality, defined as the number of survival months from the administration of first chemotherapy agent until the date of death or the end of the obser-
Elderly patients with NSCLC in the 3 Treatment Cohorts

Baseline Characteristics

Demographic and clinical data obtained from SEER included age, sex, race/ethnicity, marital status, geographic region, urban residency, ecological surrogates for educational attainment and median income, comorbidity, AJCC stage, and tumor grade according to the categories shown in Table 1. Race/ethnicity was classified as non-Hispanic white, non-Hispanic black, and other (eg, Hispanic, Asian/Pacific Islander, American Indian/Alaska Native). Race in SEER is identified from patients’ medical records and registration information, and Hispanic ethnicity in SEER is determined through a Hispanic surname algorithm that has better sensitivity than that recorded in Medicare data. To measure the burden of comorbidities, we applied the Deyo adaptation of the Charlson comorbidity index, modified to exclude cancer diagnoses, to Medicare inpatient, outpatient, and physician claims during the 12-month period extending from 13 months to 1 month before NSCLC diagnosis using lung cancer–specific weights as described by Klabunde et al. We then categorized the comorbidity score into 3 groups (0, 1, and 2).

Statistical Analysis

Differences in distribution of baseline characteristics between the bevacizumab-treated group and each of the carboplatin-paclitaxel control groups were evaluated using the \( \chi^2 \) test. The Kaplan-Meier survival method was used to estimate median survival and we tested for crude differences among the 3 groups using a log-rank test. We conducted unadjusted and multivariable Cox proportional hazards models controlling for all demographic and clinical characteristics listed in Table 1 to examine whether the addition of bevacizumab to carboplatin and paclitaxel...
improved overall survival in patients with advanced non–squamous cell NSCLC. We compared the bevacizumab-treated group with both carboplatin-paclitaxel cohorts. We used propensity score analyses\textsuperscript{22} to balance measurable confounders between the group receiving bevacizumab and each of the 2 carboplatin-paclitaxel groups. Multivariable logistic regression was used to predict treatment (bevacizumab-carboplatin-paclitaxel compared with carboplatin-paclitaxel) based on confounding covariates, including age, sex, race/ethnicity, marital status, geographic region, urban residency, tumor grading, Census tract education, median income, modified Charlson comorbidities, and AJCC stage. Each patient was then assigned an estimated propensity score, which was his/her predicted probability of receiving bevacizumab on the basis of his/her observed baseline characteristics.\textsuperscript{23,24} The cohort was then divided into 5 strata defined by quintiles of estimated propensity scores.\textsuperscript{25} Next, we used $P$ values of the $\chi^2$ test to assess whether patients' baseline characteristics were balanced across the 2 treatment groups within each stratum. Finally, Cox proportional hazards models were conducted separately within each stratum to compare overall survival of patients receiving vs not receiving bevacizumab, and then the 5 HRs estimated from each stratum were combined into an overall HR for the whole cohort.\textsuperscript{26} Cox models were also performed by applying propensity scores to adjust for group differences in 3 alternative ways: (1) regression adjustment (ie, inclusion of the propensity score as a linear predictor in the model); (2) propensity score matching, which paired bevacizumab-carboplatin-paclitaxel and carboplatin-paclitaxel patients who were similar in terms of their measurable characteristics; and (3) use of the propensity score to create stabilized weights, defined as the inverse probability of treatment weighting.\textsuperscript{27,28} The analyses were first performed on the bevacizumab combination and carboplatin-paclitaxel 2006-2007 cohorts, then repeated on the bevacizumab combination and carboplatin-paclitaxel 2002-2005 groups.

We also performed subgroup analyses for 2 characteristics that were imbalanced between treatment groups; specifically, stage IV disease, which was more prevalent in the bevacizumab group, and comorbidity, which was less prevalent in the bevacizumab group.

### Figure 1. Study Cohort

| 74,425 Patients diagnosed as having AJCC stage III/IV NSCLC in 2002-2007 |
| 14,655 Excluded (squamous cell NSCLCs) |
| 59,770 Had non–squamous cell NSCLC |
| 32,940 Excluded: |
| 8346 Age at diagnosis < 65 y |
| 5433 Diagnosis not pathologically confirmed |
| 4705 Not first and only cancer |
| 3250 Did not survive at least 30 d after diagnosis |
| 2325 Not continuously eligible for Medicare Parts A and B from diagnosis to death or 6-mo follow-up |
| 8881 Enrolled in a Medicare HMO at any point from diagnosis to death or 6-mo follow-up |
| 26,830 Eligible for inclusion |
| 14,400 Did not receive chemotherapy within 4 mo of diagnosis |
| 12,430 Treated with any chemotherapy within 4 mo of diagnosis |
| 2195 Received concurrent chemotherapy and radiotherapy |
| 10,235 Treated with first-line chemotherapy without concurrent radiotherapy |
| 664 Treated with unspecified first-line chemotherapy agents |
| 9,571 Treated with identifiable first-line chemotherapy agents |
| 5,403 Treated with chemotherapy other than carboplatin-paclitaxel alone or with bevacizumab |
| 4,168 Treated with carboplatin-paclitaxel alone or with bevacizumab |
| 318 Treated with bevacizumab-carboplatin-paclitaxel for diagnoses in 2006-2007 |
| 1,184 Treated with carboplatin-paclitaxel alone for diagnoses in 2006-2007 |
| 2,666 Treated with carboplatin-paclitaxel alone for diagnoses in 2002-2005 |

AJCC indicates American Joint Committee on Cancer; HMO, health maintenance organization; NSCLC, non–small cell lung cancer.

\textsuperscript{a}The exclusion criteria were applied sequentially as listed.

\textsuperscript{b}Nineteen patients treated with bevacizumab-carboplatin-paclitaxel in 2005 were included in the bevacizumab-carboplatin-paclitaxel group.
Sensitivity analyses evaluated the potential impact of immortal time bias and alternative strategies for treatment assignment on results. Specifically, we measured survival starting from carboplatin-paclitaxel treatment day 9, the end of the 8-day interval used to ascertain concurrent bevacizumab therapy, instead of from carboplatin-paclitaxel treatment day 1, and we expanded the interval used to identify bevacizumab concurrent administration with carboplatin-paclitaxel from 8 to 30 days, while initiating measurement of survival at day 31.

 RESULTS

Cohort Description and Baseline Characteristics

From an initial sample of 59,770 patients diagnosed as having advanced non–squamous cell NSCLC between 2002 and 2007, 26,830 patients met initial study inclusion criteria and 12,430 received chemotherapy within 4 months of diagnosis (FIGURE 1). Of these, 9,571 patients received identifiable first-line chemotherapy agents, 4,168 of whom received treatment with carboplatin-paclitaxel with or without bevacizumab. Within the study cohort, 2,666 (64%) patients had diagnoses between 2002-2005 and made up the carboplatin-paclitaxel 2002-2005 group. The remaining 1,502 patients had diagnoses in 2006-2007, and of these, 318 (21%) were in the bevacizumab-treated cohort and 1,184 (79%) were in the carboplatin-paclitaxel 2006-2007 cohort. Among patients with diagnoses in 2007, 22% were treated with the bevacizumab combination.

Characteristics of patients in the bevacizumab-carboplatin-paclitaxel, carboplatin-paclitaxel 2006-2007, and carboplatin-paclitaxel 2002-2005 groups are shown in Table 1 and were similar in most respects. Bevacizumab-treated patients were less likely to have 2 or more comorbidities (6.3% vs 16.3%; P < .001) and more likely to
have stage IV disease (82.4% vs 70.9%; P < .001) compared with the carboplatin-paclitaxel 2006-2007 group (Table 1). Similarly, compared with those in the carboplatin-paclitaxel 2002-2005 group, patients receiving bevacizumab were less likely to have 2 or more comorbidities (6.3% vs 13.0%; P = .002), more likely to have stage IV disease (82.4% vs 69.4%; P < .001), and more likely to have well- or moderately differentiated tumors (15.7% vs 10.4%, P = .01). There were no significant differences in the distribution of age, sex, race/ethnicity, marital status, income, education, SEER region, and urban residency between the bevacizumab group and each of the carboplatin-paclitaxel control groups. After adjusting for stratification of propensity scores, the balance of these observed covariates between the bevacizumab group and each of the carboplatin-paclitaxel control groups improved (eTable 1; available at http://www.jama .com). In addition, propensity score matching resulted in well-balanced bevacizumab-carboplatin-paclitaxel (n = 318) and carboplatin-paclitaxel cohorts (n = 318), all 3 of which were similar in all measurable characteristics except age at diagnosis between bevacizumab-carboplatin-paclitaxel and carboplatin-paclitaxel 2002-2005 (eTable 2), improving covariate balance from the unmatched cohorts.

### Survival Outcomes

Kaplan-Meier survival curves are shown in Figure 2. The median overall survival was 9.7 months (interquartile range [IQR], 4.4-18.6 months) for patients receiving the bevacizumab combination compared with 8.9 months (IQR, 3.5-19.3 months) for those receiving carboplatin-paclitaxel in 2006-2007, and 8.0 months (IQR, 3.7-17.2 months) for those receiving carboplatin-paclitaxel in 2002-2005. The unadjusted 1-year survival probabilities were 39.6% (95% CI, 34.6%-45.4%) for bevacizumab-carboplatin-paclitaxel vs 40.1% (95% CI, 37.4%-43.0%) for carboplatin-paclitaxel in 2006-2007 and 35.6% (95% CI, 33.8%-37.5%) for carboplatin-paclitaxel 2002-2005. Controlling for demographic and clinical characteristics in adjusted Cox proportional hazards models, we did not find a significant difference in overall survival between patients treated with bevacizumab and those treated only with carboplatin-paclitaxel in either 2006-2007 (HR, 1.01; 95% CI, 0.88-1.15) or 2002-2005 (HR, 0.94; 95% CI, 0.83-1.06) (Table 2).

None of the 4 propensity score-adjusted models demonstrated any evidence to support the superiority of bevacizumab-carboplatin-paclitaxel to carboplatin-paclitaxel. For example,
stratified analyses based on propensity scores showed no significant differences in overall survival between patients receiving bevacizumab and those receiving only carboplatin-paclitaxel in either 2006-2007 (HR, 1.01; 95% CI, 0.89-1.16) or 2002-2005 (HR, 0.93; 95% CI, 0.83-1.06). Similarly, propensity score weighting did not demonstrate a significant improvement in overall survival for the bevacizumab-treated group compared with either the carboplatin-paclitaxel 2006-2007 group (HR, 0.99; 95% CI, 0.87-1.13) or 2002-2005 group (HR, 0.93; 95% CI, 0.82-1.06) (Table 2).

Neither subgroup nor sensitivity analyses changed our essential finding that bevacizumab was not associated with a survival advantage. For example, the HR for stage IV patients treated with the bevacizumab combination compared with stage IV patients treated with carboplatin-paclitaxel in 2006-2007 was 0.96 (95% CI, 0.83-1.12) and compared with stage IV patients treated with carboplatin-paclitaxel in 2002-2005 was 0.88 (95% CI, 0.77-1.02) (Table 2). To contextualize these findings, we also evaluated the association between other measured characteristics and overall survival comparing both the bevacizumab and carboplatin-paclitaxel 2006-2007 groups and the bevacizumab and carboplatin-paclitaxel 2002-2005 groups and found that later-stage disease (stage IV vs IIIB) and higher burden of comorbidity were associated with inferior survival (Table 3).

**COMMENT**

Using data from SEER-Medicare, we compared survival outcomes for patients with advanced NSCLC of nonsquamous cell subtype who were treated with carboplatin and paclitaxel, the prevailing standard chemotherapy regimen, with or without bevacizumab. We found that in the wake of the 2006 FDA approval decision, adoption of bevacizumab was by no means universal. For patients with diagnoses in 2006 and 2007, only 20% and 22%, respectively, received bevacizumab as a component of their first-line carboplatin-paclitaxel chemotherapy regimen. In addition, we found no evidence that bevacizumab conferred a survival advantage for recipients in multivariable models that controlled for observable demographic and clinical patient attributes.

Our pattern-of-care findings in the Medicare population suggest that the medical oncology community requires therapeutic evidence specific to a particular disease prior to adoption. Medical oncologists, particularly those in private practice, may have financial incentives to administer new, expensive treatment agents if they can purchase them for less money than the CMS reimburses. Because bevacizumab is expensive and was covered by the CMS, if oncologists were subject to powerful treatment incentives as some have suggested, we would have expected to observe them in this context. That we did not observe rapid or complete uptake of bevacizumab provides some measure of reassurance that oncologists are circumspect and judicious in their use of new agents with uncertain benefit in the Medicare population.

The magnitude of the survival benefit we describe is lower than that observed in clinical trial participants. In our study, the median survival for patients treated with the bevacizumab combination was 9.7 months vs 12.3 months for participants in the ECOG 4599 trial. The carboplatin-paclitaxel patients in our study had median survival of 8.9 months (2006-2007 diagnoses) and 8.0 months (2002-2005 diagnoses) whereas in ECOG 4599 it was 10.3 months. The difference in median survival between bevacizumab and carboplatin-paclitaxel 2006-2007 was 0.8 months and between bevacizumab and carboplatin-paclitaxel 2002-2005 was 1.7 months in our observational study, which is 40% to 85% of the 2-month survival advantage obtained in ECOG 4599. This is not entirely surprising given that only 44% of carbo-

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**Table 3.** Crude Median Survival Among Patients in the 3 Treatment Cohorts and Hazard Ratios for Overall Survival Adjusting for Patient Characteristics (continued)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Crude Median Survival (IQR), mo</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modified Charlson comorbidity score</td>
<td>9.0 (4.2-20.4)</td>
<td>9.1 (3.5-20.1)</td>
</tr>
<tr>
<td>0</td>
<td>9.7 (4.2-16.7)</td>
<td>9.5 (3.4-20.3)</td>
</tr>
<tr>
<td>≥2</td>
<td>13.8 (4.9-18.4)</td>
<td>7.1 (3.6-16.3)</td>
</tr>
<tr>
<td>Level of differentiation (tumor grading)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Well/moderately</td>
<td>11.6 (6.0-35.7)</td>
<td>13.9 (5.8-30.4)</td>
</tr>
<tr>
<td>Poorly/undifferentiated</td>
<td>7.1 (3.5-14.8)</td>
<td>7.5 (3.4-18.5)</td>
</tr>
<tr>
<td>Unknown</td>
<td>9.8 (5.0-20.3)</td>
<td>8.7 (3.4-17.3)</td>
</tr>
<tr>
<td>AJCC stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIB</td>
<td>12.6 (7.6-21.8)</td>
<td>13.8 (5.5-27.9)</td>
</tr>
<tr>
<td>IV</td>
<td>8.4 (4.1-17.0)</td>
<td>7.4 (3.2-15.7)</td>
</tr>
</tbody>
</table>

Abbreviations: AJCC, American Joint Committee on Cancer; IQR, interquartile range; SEER, Surveillance, Epidemiology, and End Results.

a Carboplatin-paclitaxel treatment for diagnoses in 2006-2007 when bevacizumab was approved by the US Food and Drug Administration for non–small cell lung cancer (NSCLC).

b Carboplatin-paclitaxel treatment for diagnoses in 2002-2005 when bevacizumab was not available (2002-2003) or not approved for NSCLC treatment.

c The income and education quartiles were constructed when comparing the bevacizumab-carboplatin-paclitaxel group with each of the carboplatin-paclitaxel control groups; thus, the cutoff values were not the same across these groups.

d Modified Charlson comorbidity score was constructed by applying the Deyo adaptation17 of the Charlson comorbidity index, modified to exclude cancer diagnoses, to Medicare inpatient, outpatient, and physician claims during the 12-month period extending from 13 months to 1 month before NSCLC diagnosis using lung cancer-specific weights as described by Klabunde et al.19,20

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though it is likely to be more representative of NSCLC in the United States,12 although more than one-third were older than 75 years at diagnosis. The marginally lower median survival rates in our observational cohort compared with either the complete group or elderly subgroup of the efficacy cohort may also be attributed to differences in clinical factors such as performance status and baseline lung function that cannot be ascertained from SEER-Medicare data.

Researchers have called for prospective trials specifically designed for elderly patients to better define the role of intensive cancer treatments that are routinely demonstrated to have superiority in clinical trials that recruit patients who are younger and/or healthier than the general population of patients with the index malignancy.34-36 However, elderly-specific trials with bevacizumab face practical barriers. For example, Merza et al37 studied 106 elderly male patients diagnosed as having advanced NSCLC at a Veterans Administration medical center and found that only 10% of patients were candidates for bevacizumab after applying exclusion criteria used in ECOG 4599 and another bevacizumab combination trial. Our study supplements the nonsignificant results from the subset analyses of older patients in ECOG 459938 and substantiates prevailing practice patterns that demonstrate that oncologists are circumspect about using bevacizumab for their elderly patients with NSCLC.

Our study must be interpreted in the context of limitations inherent to all observational studies as well as those that rely on administrative data sources such as Medicare. First, the study was limited to Medicare fee-for-service beneficiaries who were aged 65 years or older and living in a SEER region at diagnosis. This cohort may not be representative of all patients with non–squamous cell NSCLC in the United States, although it is likely to be more representative than the sample of clinical trial participants. Second, SEER-Medicare lacks essential clinical details, such as the presence of molecular biomarkers, performance status, and baseline pulmonary function, which may be associated with the selection of chemotherapy agents, survival, or both. However, the inability to identify patients with poor baseline lung function and limited performance status or other clinical contraindications to bevacizumab such as significant hemoptysis and brain metastases would be expected to widen rather than narrow the apparent gap in survival between patients receiving bevacizumab-carboplatin-paclitaxel vs carboplatin-paclitaxel. In an observational cohort, patients with relative contraindications to bevacizumab are more likely to be included in the carboplatin-paclitaxel cohort, and this should increase the survival advantage of bevacizumab-carboplatin-paclitaxel relative to carboplatin-paclitaxel. That we did not observe this lends credence to our finding that there is no sizeable benefit from adding bevacizumab to carboplatin-paclitaxel in the Medicare population. Third, because we have NSCLC diagnoses only through 2007, the sample size for bevacizumab-carboplatin-paclitaxel–treated patients was small, and we cannot exclude the possibility that more recent data and/or a larger sample would yield different results. Fourth, differences in second- and third-line chemotherapy between study groups may have contributed to survival outcomes; the overall survival might favor the group that had a higher percentage of patients receiving further lines of chemotherapy. Finally, although we used statistical techniques to mitigate the potential for imbalance between our cohorts based on measured prognostic factors, the potential for selection bias based on unmeasured factors that predisposed patients to be included in a particular treatment group cannot be excluded.

In conclusion, our analyses suggest that the addition of bevacizumab to carboplatin and paclitaxel is not associated with demonstrable improvement in overall survival in the Medicare population. In the future, malignancies like NSCLC that disproportionately affect elderly patients or where the CMS covers a large proportion of treatment costs, negotiations with pharmaceutical sponsors of pivotal trials might mandate adequate representation of elderly patients and/or preplanned subgroup analyses relevant to the Medicare population. Absent this information, clinicians will need to rely on efficacy data from subgroup analyses randomized trials, observational data such as this report, and their clinical judgment to make treatment recommendations. Given that neither subgroup analyses from efficacy studies nor observational data analyses identify a benefit for adding bevacizumab to standard carboplatin-paclitaxel therapy, bevacizumab should not be considered standard of care in this context. Clinicians should exercise caution in making treatment recommendations and should use bevacizumab judiciously for their older patients.

Author Contributions: Dr Schrag had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Zhu, Sharma, Schrag.

Acquisition of data: Schrag.

Analysis and interpretation of data: Zhu, Sharma, Gray, Chen, Weeks, Schrag.

Drafting of the manuscript: Zhu, Schrag.

Critical revision of the manuscript for important intellectual content: Sharma, Gray, Chen, Weeks.

Statistical analysis: Zhu, Sharma.

Obtained funding: Weeks, Schrag.

Administrative, technical, or material support: Zhu, Sharma, Weeks, Schrag.

Study supervision: Zhu, Schrag.

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