

# Metastatic Non–Small Cell Lung Cancer: Costs Associated With Disease Progression

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**L**ung cancer is the leading cause of cancer death in the United States and worldwide<sup>1,2</sup> and was the third most frequently diagnosed cancer in the United States in 2002.<sup>1</sup> More than 60% of all patients with non–small cell lung cancer (NSCLC) present with metastatic or locally advanced disease on initial diagnosis.<sup>1</sup> Unfortunately, patients with advanced metastatic disease typically achieve only modest improvements in survival and palliation of symptoms with chemotherapy.<sup>3,5</sup>

Because clinical improvement with standard chemotherapy alone is limited in advanced NSCLC, combinations of treatment approaches, including surgery, radiation therapy, chemotherapy, immunotherapy, and targeted agents, are being evaluated, as well as new systemic treatments.<sup>6</sup> Therefore, patients are receiving additional and possibly more intensive treatments, which may increase their health expenditures and cost of care. Economic studies<sup>7–10</sup> have demonstrated that the cost burden of lung cancer on the healthcare system is substantial. Annual US direct costs of lung cancer were estimated at \$4.9 billion in 1996.<sup>10</sup> Retrospective studies<sup>7–9</sup> using US managed care claims reported a total cost of at least \$45,897 for patients with lung cancer. There is little evidence to show whether these costs are driven by improved survival, disease progression, or progression-free survival.

Based on overall survival or progression-free survival, clinical trials have established the efficacy of chemotherapy agents in NSCLC treatment.<sup>11,12</sup> Economic evaluations of chemotherapy agents have used the progression-free survival end point for determining the cost-effectiveness of specific agents or have focused solely on the cost effect associated with initial treatment of NSCLC.<sup>13–15</sup> Therefore, direct cost analyses of disease progression as a clinical outcome among patients with NSCLC are limited. Given the rising rates of cancer prevalence, the influence of treatment guidelines and quality-of-care initiatives, and the increasing focus on treatment reimbursement by managed care plans, it is more important than ever to elucidate the costs associated with disease progression to better understand the value of extending progression-free survival time. The present study was conducted to estimate the real-world cost burden of disease progression among patients with advanced metastatic NSCLC.

**Objective:** To compare direct costs of care among patients having advanced non–small cell lung cancer (NSCLC) with versus without disease progression following first-line chemotherapy.

**Study Design:** A retrospective study was conducted among patients with stage IIIB or IV metastatic NSCLC diagnosed between January 1, 2001, and May 30, 2005.

**Methods:** Progression was defined as a change in chemotherapy regimen and radiologic confirmation of tumor growth. Total direct costs after diagnosis were computed monthly and were aligned chronologically between patients with and without progression to determine the mean costs for the 3 months after progression. Multivariate linear regression analysis estimated predictors of progression costs.

**Results:** Among 306 patients with NSCLC who received chemotherapy, 108 patients experienced documented progression. Total cost of care from progression to death or end of study was \$42,066. The mean direct 3-month postprogression cost of care was \$31,129 for patients with progression compared with \$18,802 for patients with stable disease, yielding an incremental cost of \$12,327.

**Conclusion:** Patients with metastatic NSCLC who experience progression have significantly greater costs than similar patients with stable disease.

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## METHODS

A retrospective observational study was conducted to quantify the di-

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rect cost of care among patients having advanced NSCLC with disease progression within the Henry Ford Health System (HFHS), Detroit, Michigan. A secondary objective of the study was to determine the incremental costs of disease progression compared with the costs of similar patients having NSCLC without disease progression. The HFHS is a large integrated healthcare system located in the greater metropolitan area of Detroit, and it provides acute, primary, specialty, and tertiary care to approximately 400,000 individuals. Annually, care provided within the HFHS includes 2.5 million patient contacts, 40,000 surgical procedures, and 40,000 hospital admissions. The catchment population of the HFHS is ethnically diverse (approximately 35% African American) and represents various payer groups, including a health maintenance organization (50%), BlueCross (12%), other commercial payers (21%), Medicare (10%), Medicaid (2%), and private payers (4%). The HFHS cancer registry was used to identify patients with NSCLC, and this data source provided baseline characteristics about patient age, race/ethnicity, and cancer variables (including disease stage and initial treatment). Physician diagnoses, disease progression, and survival status were extracted from the electronic medical records at HFHS. Patient charge data were extracted from the administrative electronic data files of the integrated health system.

### Patient Population

The HFHS cancer registry was used to identify all patients with stage IIIB or IV NSCLC diagnosed between January 1, 2001, and May 30, 2005. Eligible patients were followed forward from diagnosis until May 30, 2006, or death for the occurrence of disease progression and for the cost of care after progression. With these time frames, it was assumed that a patient who was diagnosed as having stage IIIB or IV NSCLC on May 30, 2005 (the end of the patient identification period) would have approximately 8 months to observe disease progression and then 3 to 4 months after progression to estimate total direct costs. This time frame was deemed adequate based on the median survival time of 8 to 10 months for patients with advanced NSCLC.<sup>1</sup> Physician diagnoses for the 12 months before NSCLC diagnosis were obtained from the HFHS administrative databases and were used to calculate a comorbidity score using the Charlson Comorbidity Index.<sup>16</sup> Patients with multiple active cancers (other cancer diagnosed within 12 months of the NSCLC diagnosis) were excluded from the study because the cost of NSCLC disease progression could not be isolated from costs related to the other cancers. The study was approved by the HFHS institutional review board, and all data were in compliance with the Health Insurance Portability and Accountability Act.

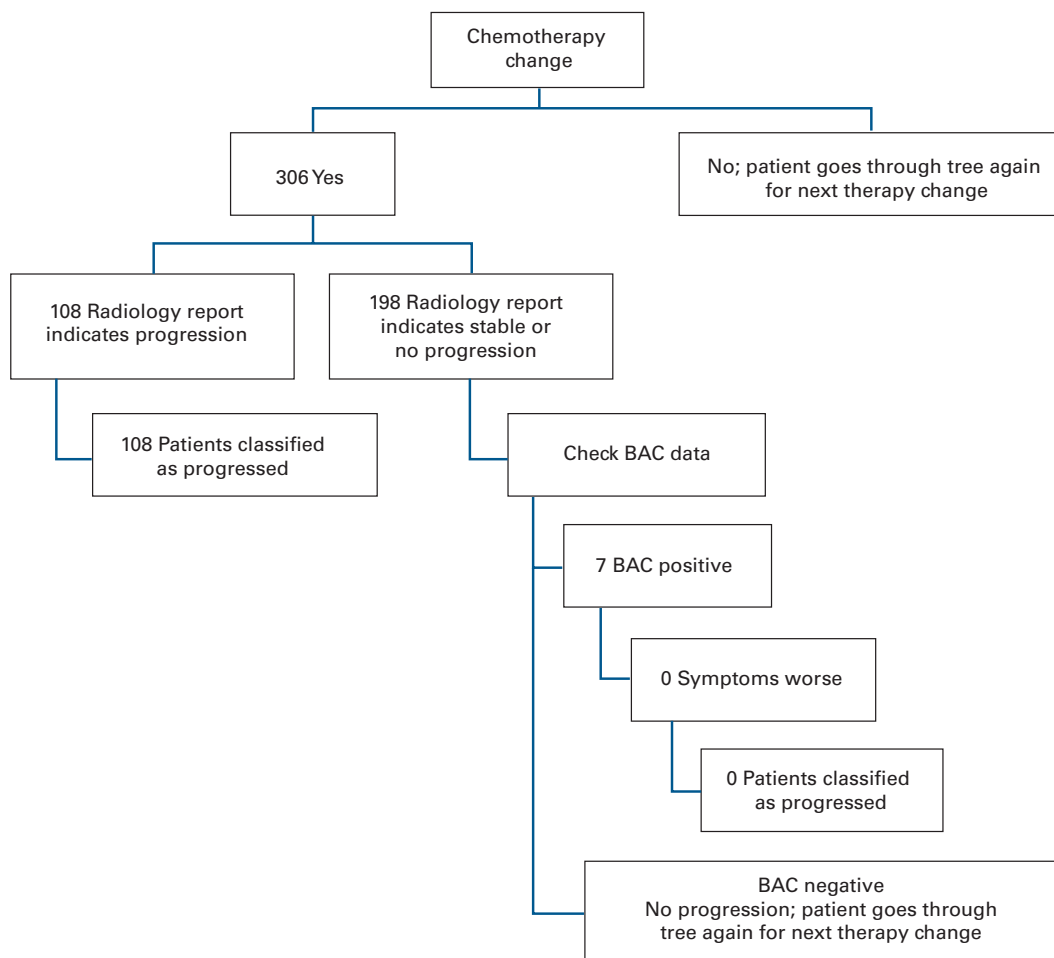
### Disease Status

Disease progression was determined by medical record abstraction using the HFHS electronic medical records. In this study, progression of metastatic NSCLC was defined as a change in chemotherapy regimen accompanied by radiology reports documenting tumor growth. Patients starting first-line chemotherapy after their cancer diagnosis were identified and followed forward through their medical records to observe disease progression. Both criteria (therapy change and radiologic confirmation) had to be met for the patient to be classified as having disease progression. The only exception to this was among patients with bronchioloalveolar carcinoma (BAC), who were required to have a change in chemotherapy regimen accompanied by worsening of symptoms (pain or shortness of breath) instead of radiologic confirmation because clinical progression among these patients does not present radiographically. The oncologist's medical record notes were abstracted to determine if there was an increase in symptom frequency or severity for the patients with BAC. Change in chemotherapy regimen was defined as 1 or more chemotherapy agents being discontinued, switching of agents, or addition of a new agent to the current regimen. Treatment discontinuation included patients who stopped their current chemotherapy treatment and did not restart the same treatment regimen within 6 weeks. If a patient discontinued his or her chemotherapy treatment for less than 6 weeks and returned to the same treatment regimen, it was classified as treatment continuation and not chemotherapy change because the break in therapy may have been due to a nontreatment-related reason (eg, vacation). For those patients with a chemotherapy change, their radiology report around the time of the chemotherapy change ( $\leq 21$  days before or  $\leq 14$  days after the chemotherapy change) was reviewed to determine if the radiologist reported tumor size increase, disease progression, new lesions versus stable disease, no tumor growth, or no new lesions. The algorithm for defining disease progression among patients with metastatic NSCLC is shown in **Figure 1**.

### Cost Parameters

Patients with and without disease progression were included in the cost analyses. The analysis on charges of care included total charges of cancer care and noncancer care for hospitalizations, physician office visits, ambulatory clinic visits and procedures, laboratory tests, and pharmacy. Pharmacy charges included all lines of chemotherapy and drug treatment for adverse effects, if present, as well as all other prescription medications. The charges were multiplied by the HFHS cost-charge ratio to ascertain costs. Costs for the patients with disease progression were summed from the date of

■ **Figure 1.** Patient Flow Diagram for Identifying Non–Small Cell Lung Cancer Disease Progression



BAC indicates bronchioloalveolar carcinoma.

first progression to death or end of study (March 31, 2006) to quantify the total cost of care after progression for patients with disease progression. Also, the incremental costs associated with disease progression were estimated for the 3 months after progression. Three-month costs were computed to estimate the economic burden of disease progression because of the short survival time of patients with progressive metastatic disease. Longer periods would exclude many patients who do not survive the full period, and the cost estimate would be biased toward longer survival. To compute the 3-month costs, the monthly mean direct costs for each month after diagnosis were estimated for patients without progression. Only patients surviving through the end of each month were included in each monthly estimate. These mean monthly costs were then matched chronologically to the same 3 months after diagnosis for each patient

with disease progression so that the costs were from the same postdiagnosis period. For example, if a patient progressed at the beginning of the sixth month after diagnosis, costs for months 6, 7, and 8 were summed for the comparison patients to obtain that patient's postprogression costs. The chronologic match of cost-months was also performed to control for severity of illness among patients with and without disease progression. As a comparison cost, we summed the mean monthly costs for the nonprogression patients in months 6, 7, and 8 after diagnosis. If a patient progressed in the middle of a month (eg, halfway through the sixth month after diagnosis), weighted portions of the nonprogression mean costs for months 6, 7, 8, and 9 after diagnosis were used to compute the comparison cost, as shown in the following example:  $0.5(\text{month 6 cost}) + \text{month 7 cost} + \text{month 8 cost} + 0.5(\text{month 9 cost})$ .

**Table 1.** Demographic and Clinical Characteristics of Patients With Stage IIIB or IV Non–Small Cell Lung Cancer (NSCLC) Who Received or Did Not Receive Chemotherapy as First-line Therapy

Characteristic	Patients Receiving Chemotherapy (n = 306)	Patients Not Receiving Chemotherapy (n = 263)
Age, mean (SD), y	64.0 (11.1) <sup>a</sup>	67.9 (11.7)
Male sex, No. (%)	171 (55.9)	151 (57.4)
White race/ethnicity, No. (%)	191 (62.4) <sup>a</sup>	104 (39.5)
<b>Charlson Comorbidity Index score, No. (%)</b>		
1-4	150 (49.0) <sup>a</sup>	109 (41.4)
5-8	69 (22.5)	57 (21.7)
≥9	87 (28.4)	97 (36.9)
<b>Tumor stage, No. (%)</b>		
IIIB	100 (32.7)	73 (27.8)
IV	206 (67.3)	190 (72.2)
<b>Length of follow-up from NSCLC diagnosis to death or end of study, mean (SD), d</b>		
Survival ≤6 mo, No. (%)	203 (66.3) <sup>a</sup>	59 (22.4)

<sup>a</sup>*P* < .05.

### Statistical Analysis

Descriptive statistics (mean and standard deviation for continuous variables and percentage of patients for categorical variables) were used to report the study population characteristics. A multivariate linear regression model was constructed, and tests for nonlinearity were conducted to adjust the estimates of total direct cost of disease progression for known confounders. Potential confounding variables were age, sex, race/ethnicity, comorbidity score, type of health insurance, and duration before progression. A model with the natural log of cost as the dependent variable was also constructed. A Kaplan-Meier curve was constructed to determine the mean time to disease progression. Two-sample *t* tests were used to compare costs between patients with and without disease progression. The difference between costs for the patients with disease progression versus those without progression was considered the incremental cost of care for the 3 months after progression. All statistical analyses were performed using SAS software (version 9.1; SAS Institute, Inc, Cary, North Carolina). All statistical testing was 2-sided, and *P* < .05 was considered a priori significant.

## RESULTS

There were 569 eligible patients with stage IIIB or IV NSCLC, of whom most were male (57%) and of white race/

ethnicity (52%), with a mean age of 66 years. Only 7 patients had BAC. Of the eligible patients, 306 (54%) received chemotherapy. Patients who received chemotherapy were significantly younger, had fewer comorbid conditions, were mostly of white race/ethnicity, and had longer survival than patients who did not receive chemotherapy (*P* < .05) (Table 1).

Among 306 patients receiving chemotherapy, 159 switched agents, and 147 discontinued their chemotherapy. The primary chemotherapy regimen was doublet therapy (70%), with carboplatin and paclitaxel as the most common regimen. Fewer than 10% of patients received any one of the other agents. Approximately 6% of patients had triplet therapy as their first-line regimen. There were 159 patients who had a second line of therapy, which was mostly monotherapy (85%), and docetaxel was the most frequently prescribed agent (29%), followed by gefitinib (16%). In

addition, 79 patients had a third line of chemotherapy, and gefitinib (33%) was the most frequently prescribed agent, followed by gemcitabine hydrochloride (14%).

The 306 patients had their radiology reports reviewed to determine if disease progression occurred (Figure 1). Radiologic confirmation of disease progression around the time of the chemotherapy change was observed in 108 patients (35%). The mean time to disease progression was estimated at 587 days. The mean total cost of care from first progression to death or end of study (including all lines of chemotherapy and treatment of adverse effects, if present) was \$42,066 (95% confidence interval [CI], \$34,445-\$49,687; median, \$26,349) for the patients who had disease progression (Figure 2). The mean duration of survival after progression was 110 days. Inpatient costs (95% CI, \$17,318-\$26,481; median, \$16,413) and outpatient costs (95% CI, \$12,832-\$21,672; median, \$6696) were the largest component costs of care. Using a multivariate regression model to control for age, sex, race/ethnicity, Charlson Comorbidity Index, preprogression duration, and insurance coverage, the total costs of care after progression were found to vary only with younger age (<40 years). All other variables in the regression model were not significant (*F* = 1.84, *R*<sup>2</sup> = 0.26, *P* > .05). Estimates from the model with the natural log of cost as the dependent variable did not differ from the linear model estimates.

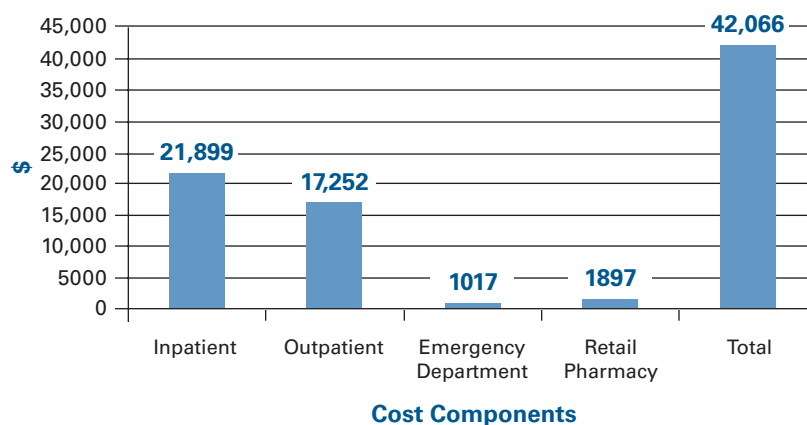
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Patients with versus without disease progression were compared to ascertain the incremental cost of disease progression in the 3 months following the first progression. Patients with disease progression were significantly younger and were more likely to have stage IV NSCLC than patients without progression ( $P < .05$ ) (Table 2). Patients with disease progression also had a shorter length of follow-up (305 days) compared with patients without progression (486 days) ( $P < .05$ ). The total cost of care for the 3 months after progression among patients with disease progression was \$31,129 (95% CI, \$25,346–\$36,913) compared with \$18,802 (95% CI, \$17,481–\$20,123) for the same time period among patients without disease progression ( $P < .05$ ) (Figure 3). Therefore, the mean incremental cost of care for the 3 months following progression was \$12,327. Treatment costs for patients with disease progression declined after cancer diagnosis, but the difference in costs between patients with versus without disease progression was stable in the months during which most patients progressed (74% had disease progression 3–9 months after cancer diagnosis).

## DISCUSSION

In a terminal disease such as NSCLC, the ultimate treatment goal for patients is improvement in overall survival, and therapies that improve survival and quality of life at any point in the disease course are critical. However, current oncology trials often use progression-free survival as the primary study end point, and it is important to understand the importance of progression-free survival as a clinical benefit to the patient, as well as the implications of improvement in progression-free survival on cost of care. This study provides unique information on the cost associated with disease progression from a real-world perspective. The study population was large ( $N = 569$ ), which facilitated the identification of disease progression in an adequate sample size. The availability of electronic medical records also made it feasible to extract information from the radiology reports and from oncologists' notes to ascertain disease progression, which is unavailable in health claims–based studies. Thirty-

**Figure 2.** Direct Cost of Care From First Progression to Death/End of Study Among Stage IIIB or IV Non–Small Cell Lung Cancer Patients Who Experienced Disease Progression ( $n = 108$ )



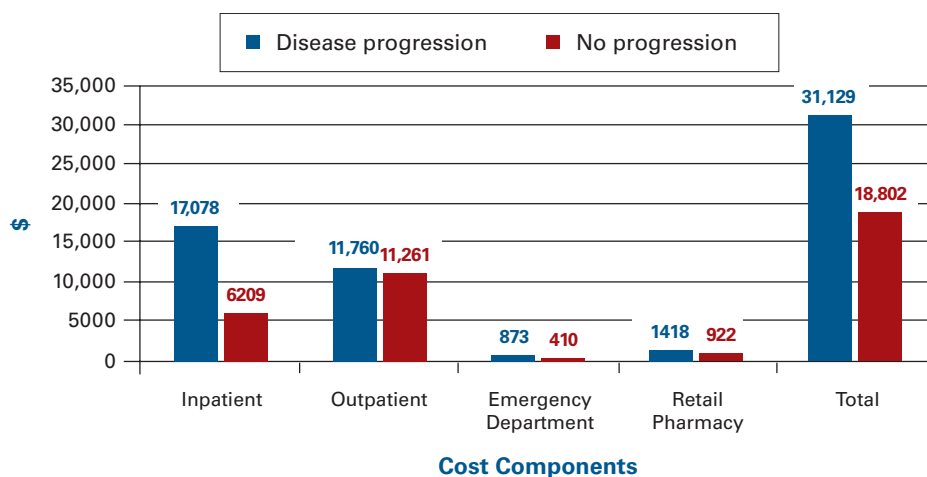
**Table 2.** Demographic and Clinical Characteristics of Patients With Stage IIIB or IV Non–Small Cell Lung Cancer (NSCLC) Who Did or Did Not Experience Disease Progression

Characteristic	Patients With Disease Progression ( $n = 108$ )	Patients Without Disease Progression ( $n = 198$ )
Age, mean (SD), y	61.8 (11.2) <sup>a</sup>	67.9 (11.7)
Male sex, No. (%)	59 (54.6)	112 (56.6)
White race/ethnicity, No. (%)	63 (58.3)	128 (64.6)
Charlson Comorbidity Index score $\geq 7$ , No. (%)	52 (48.1)	93 (47.0)
Tumor stage IV, No. (%)	81 (75.0) <sup>a</sup>	125 (63.1)
Length of follow-up from NSCLC diagnosis to death or end of study, mean (SD), d	305.4 (238.2) <sup>a</sup>	486.2 (420.9)
Survival $\leq 6$ mo, No. (%)	64 (59.3)	139 (70.2)

<sup>a</sup> $P < .05$ .

five percent of patients with stage IIIB or IV NSCLC had disease progression after their first course of chemotherapy as determined by a change in chemotherapy regimen and by radiologic confirmation of tumor growth. In this study, treatment of patients with disease progression is costly, exceeding \$42,000 during a mean of 110 days at a mean cost of \$382 per day. The incremental cost of care was also substantial for the 3 months following disease progression. Patients with disease progression had costs exceeding \$12,000 more than the amount incurred for patients having advanced NSCLC without disease progression during the same period after diagnosis. This difference was statistically significant. Disease progression is an important clinical event that has potential for significant cost implications.

■ **Figure 3.** Direct Costs for 3 Months After First Progression Among Advanced Non-Small Cell Lung Cancer Who Had Disease Progression and Comparably Time-aligned Cost for Patients Without Disease Progression



Studies assessing cost of disease progression (prostate cancer)<sup>17</sup> or cost of disease recurrence (breast cancer)<sup>18</sup> in other tumor types have been published. Both studies used data from the HFHS and reported that patients with progression or recurrence required more costly care than patients who did not develop progression. For prostate cancer, metastatic progression resulted in charges of \$92,523 compared with \$58,036 for patients without progression during 1 year.<sup>17</sup> In breast cancer, patients who had contralateral, locoregional, and distant recurrences had higher mean total care charges by \$43,803, \$66,927, and \$102,504, respectively, compared with patients without recurrence.<sup>18</sup>

To our knowledge, there are no studies that have examined the cost of disease progression in patients with NSCLC. However, a retrospective study of managed care claims by Kutikova and colleagues<sup>7</sup> reported markedly increased cost associated with lung cancer treatment failure (\$10,370 per month in initial treatment phase costs and \$8779 more per month after starting the secondary or terminal care phase than patients requiring only initial treatment). Although the study methods are different, the study by Kutikova et al and the

because the authors did not confirm treatment failure with radiologic evidence of disease progression. These published studies in addition to the present study demonstrate that disease progression is costly and warrants more attention.

The present study has some limitations. The study population comprised patients from HFHS, which serves the greater Michigan and Ohio areas and may not be representative of patient populations with advanced NSCLC in other regions of the United States or reflect the variability in national treatment patterns and resource utilization. The definition of disease progression was conservative through its requirement of including both chemotherapy regimen change and radiologic confirmation. This strict definition may not reflect how disease progression is typically determined in clinical practice. However, this method was used to ensure the identification of true cases of disease progression and to limit the number of false positives within the limits of a retrospective database study. Patients may have been classified as “without progression” if a radiology report was not recorded around the time of the chemotherapy regimen change, but this would make the incremental cost estimate more conservative, and the actual cost of disease progression may be higher than our estimate. Some patients may have been classified as “without progression” but had disease progression after the study period, particularly patients who were diagnosed as having advanced NSCLC close to the end of the patient identification period (March 31, 2005). The study

present study provide evidence that costs are high for patients with advanced NSCLC who fail treatment or experience disease progression. The 2 studies cannot be directly compared because the study by Kutikova and colleagues investigated all types of lung cancer and not advanced-stage NSCLC, as the present study did. Also, their findings are based on treatment failure, which may include patients with disease progression but also may involve patients with therapy tolerability problems

### Take-away Points

This study provides unique information about the cost of disease progression among patients with metastatic non-small cell lung cancer (NSCLC).

- Disease progression among patients with advanced NSCLC is costly and will affect health plan budgets within a short period.
- These findings highlight the opportunity to communicate the importance of disease progression as a clinical outcome and its effect on cost of care.
- Patients with metastatic NSCLC who experienced progression had significantly greater costs than similar patients with stable disease.

design allowed approximately 9 months for the observation of disease progression among these patients; therefore, few patients may have been misclassified because the survival time is short for advanced NSCLC. The cost estimate of disease progression during the total period (until death or end of study) may be affected by a survival bias in which very sick patients who die quickly after diagnosis do not have an opportunity to contribute to the costs as much as less sick patients who survived until the end of the study. Given the time frame for the study (January 1, 2001, to March 31, 2006), there were few patients (n = 14) treated with the newer treatments (Avastin, Tarceva, or Alimta), and it is unknown whether disease progression rates would be different for patients with advanced NSCLC who are treated with these agents.

## CONCLUSIONS

Disease progression among patients with advanced NSCLC is costly and will affect health budgets within a short period. These findings highlight the opportunity to communicate the importance of disease progression as a clinical outcome and its effect on cost of care. Patients with metastatic NSCLC who experienced progression had significantly greater costs than similar patients with stable disease. New therapies that postpone progression may alleviate some of the incremental cost burden.

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**Authorship Information:** Concept and design (KMF, JMB, JK); acquisition of data (KMF); analysis and interpretation of data (KMF, JMB, JK); drafting of the manuscript (KMF, JMB, JK); critical revision of the manuscript for important intellectual content (KMF, JMB, JK); statistical analysis (JMB); obtaining funding (JK); and supervision (JK).

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