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(Article begins on next page)

The Value of Targeted Therapies in Lung Cancer

A dissertation presented

by

Dorothy Romanus

to

The Committee on Higher Degrees in Health Policy

In partial fulfillment of the requirements
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The Value of Targeted Therapies in Lung Cancer

Abstract

The goal of this dissertation was to examine the realized value of targeted therapies in routine care and to identify opportunities for improving the return on medical spending for these technologies.

Chapter 1 investigated the value of targeted therapies in lung cancer patients who were treated in routine care. This observational, claims-based analysis used propensity score, and instrumental variable methods, combined with a Kaplan Meier Sample Average estimator to calculate lifetime costs and life expectancy. An incremental comparison showed that the realized value of targeted therapies in routine care was unfavorable relative to chemotherapy treatment. Subgroup analyses revealed that initial erlotinib therapy yielded effectiveness results that are substantially lower than efficacy survival outcomes in molecularly guided trials. Our results indicated that in routine care, chemotherapy was the most cost effective strategy. The unexpectedly low outcomes with first-line erlotinib suggested that some of the value of this treatment was not being realized in practice.

Chapter 2 examined the practice patterns of targeted therapies and utilization of predictive biomarker testing in routine care to better understand the observed gaps between trial-based and 'real-world' outcomes with these agents. In our nationally representative cohort of lung cancer patients, we found that the vast majority of patients

did not undergo molecular testing to inform first-line therapy. Our prediction models for biomarker screening and first-line treatment suggested that phenotypic enrichment criteria guided selection for testing and initiation of erlotinib therapy. Since clinical characteristics do not adequately discriminate between mutation positive and wild type tumors, these practices signal the need for wider dissemination of biomarker screening to accurately target patients towards improving therapeutic gains with erlotinib.

Chapter 3 assessed the cost-effectiveness of multiplexed predictive biomarker screening to inform treatment decisions in lung cancer patients. Using a micro-simulation model to evaluate the incremental value of molecularly guided therapy compared to chemotherapy in unselected patients, we found that personalized therapy is a cost effective strategy. Our results indicated that better value of targeted therapies in lung cancer is achievable through molecularly guided treatment.

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To Piotr, Alex and Nelia

Chapter 1 The Value of Targeted Therapy in Lung Cancer: An Observational Analysis of Elderly Medicare Population

1.1 Introduction

The burden of lung cancer is large both in terms of its impact on those afflicted by the disease and in economic terms. Lung cancer is the leading cause of cancer-related mortality, with 160,000 deaths estimated to occur nationwide in 2014, which represents 27% of all cancer deaths.[1] In 2010, medical spending for cancer reached \$125 billion, with 10% attributable to lung cancer care alone. Over the next decade, these costs are projected to grow by 27% taking into account only the aging of the population.[2] Structural changes such as technology advances will put further inflationary pressure on the growing costs for cancer care.

The introduction of targeted therapies in the treatment of advanced non-small cell lung cancer (NSCLC) represents an innovation that has profoundly changed the landscape of prognosis in select patients, but these treatments come with a high price tag.[3-5] The two targeted therapies that gained approval by the Federal Drug Administration (FDA) for treatment of patients with locally advanced or metastatic NSCLC before 2013 are bevacizumab and erlotinib. The latter is an orally administered epidermal growth factor tyrosine kinase inhibitor (EGFR TKI).[6] It has demonstrated a remarkable efficacy in patients whose tumors harbor *EGFR* drug sensitizing mutations compared to chemotherapy alone, with median progression free survival (PFS) of 9.4 vs. 5.2 months (p-value <0.0001).[7] The role of *EGFR* mutations as a predictive biomarker for response to erlotinib has been clearly elucidated, but in practice,

molecular screening is widely underutilized.[8, 9] Bevacizumab was approved for initial treatment of advanced, non-squamous NSCLC, based on a phase III randomized clinical trial (ECOG 4599), which demonstrated a statistically significant but clinically modest median overall survival (OS) benefit of 2 months compared to chemotherapy alone.[10, 11] Trial-based results, however, may not be directly generalizable to the majority of patients who are treated in the community, since trials are conducted under strictly controlled protocols to increase the internal validity of findings. Patients treated in clinical trials generally constitute a highly selected, healthier and younger group compared to the general lung cancer population.[12, 13] Case in point is a recent analysis of non-trial patients with advanced NSCLC, which compared survival outcomes of carboplatin and paclitaxel chemotherapy combination with and without the addition of bevacizumab. Unlike the earlier ECOG trial findings, this observational analysis of an elderly patient cohort indicated no significant OS benefit for the bevacizumab combination (hazard ratio of 1.01 (95% CI, 0.89-1.16)).[11, 14]

There is an increasing awareness among the oncology community and policy makers that while some targeted therapies hold the promise of substantial outcome improvements in cancer, they are associated with high costs. Bevacizumab costs \$7,400 for a 3-week cycle to treat an average patient.[15] The corresponding cost for erlotinib is around \$3,400.[16] While the acquisition costs for these drugs are high, it is important to examine not just the costs of the drug but also the total costs associated with management of patients who receive these therapies, in tandem with the outcomes. Traditional economic analyses that estimate the value of medical

interventions to inform decision-makers have been based on efficacy data from trials. To date, the cost-effectiveness of both erlotinib and bevacizumab in NSCLC has been evaluated using these efficacy endpoints.[17, 18] In contrast, an evaluation based on routine care that incorporates contemporary practice patterns and effectiveness outcomes may help illuminate the actual *realized* value of these innovations. Such a population based analysis may help inform decisions surrounding translational research funding and coverage policies.

To assess the value of targeted therapies in routine care, we compared the relative cost effectiveness of management with best supportive care (BSC) versus treatment with chemotherapy alone or with targeted therapy among patients with advanced NSCLC. The analysis was done from a payer perspective in the United States using a lifetime horizon.

1.2 Methods

1.2.1 Data Sources

We used data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program linked to Medicare claims. The SEER program collects information from 17 cancer registries, which cover approximately 28% of the US population.[19] SEER captures information on cancer sites, histology, stage, grade, and dates of diagnosis and death, as well as patient demographic characteristics for all persons diagnosed with a cancer residing in one of the cancer registries. SEER data for patients with diagnoses from January 1, 2007 through December 31, 2009, matched to Medicare claims data from January 1, 2006, through December 31, 2010 were

available for patients with fee-for-service (FFS) coverage. Information from claims for inpatient and outpatient hospital, skilled nursing facility, home health agency, and hospice care, as well as physician services, prescription drugs and durable medical equipment was included in the analysis.

1.2.2 Study participants

Patients with pathologically confirmed non-squamous, stage IV NSCLC diagnosed between January 1, 2007 and December 31, 2009 were included. Stage at diagnosis based on the SEER derived staging algorithms was used to identify patients with advanced disease. To increase the homogeneity of patients, we excluded patients who underwent primary cancer surgery.[20] Patients were also excluded if they had other cancers diagnosed either before or after the index NSCLC diagnosis (to avoid chemotherapy misclassification bias). Patients enrolled in either a health maintenance organization (HMO), or only in part A or B Medicare at any time during the observation period, starting 12 months prior to diagnosis and ending at death or last follow up, were excluded to ensure a complete history of claim records. The primary comparison groups were based on receipt of any targeted therapy (bevacizumab, erlotinib), with or without chemotherapy, starting from index diagnosis (Figure 1.1). Specifically, we compared three groups: 1) targeted treatment group, which comprised of patients who were treated with bevacizumab or erlotinib, with or without chemotherapy, at some point after diagnosis of stage IV NSCLC ; 2) chemotherapy group, consisting of patients who received chemotherapy alone and no targeted therapy at any point after diagnosis; 3) remaining patients were categorized to the best supportive care (BSC) group, if there was no evidence of systemic therapy receipt (chemotherapy or targeted therapy).

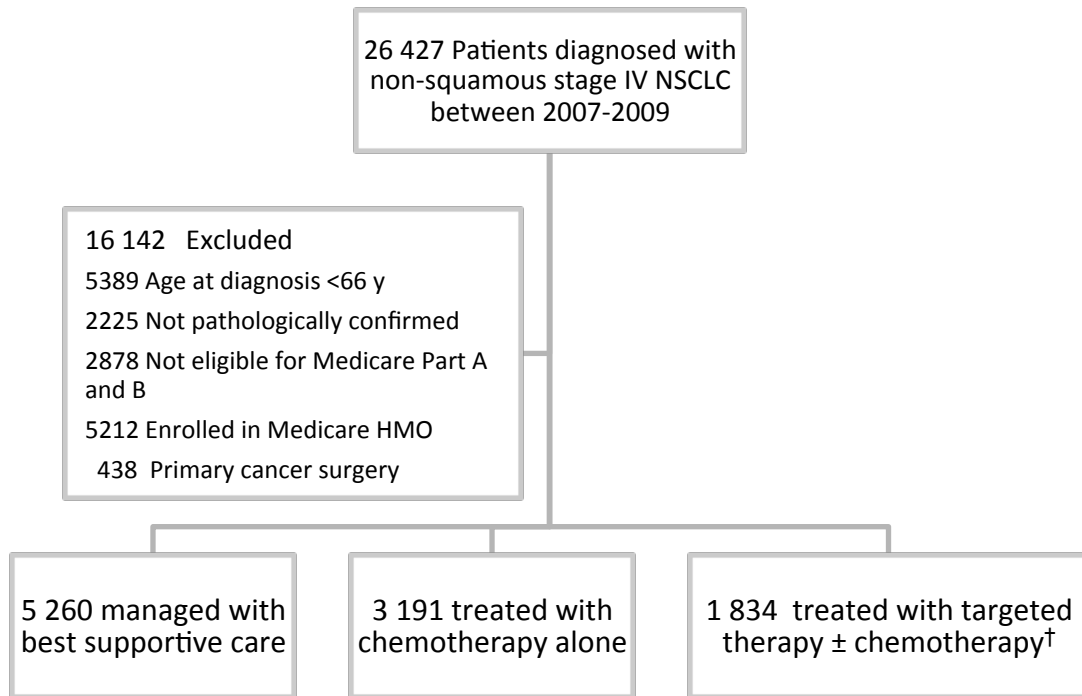


Figure 1.1. Flow diagram of study cohort

NSCLC, non-small cell lung cancer

†targeted therapy includes bevacizumab and erlotinib

1.2.3 Treatment Classification

We identified systemic therapy use from Medicare claims. Claims for individual drugs and therapy administration were flagged using International Classification of Disease Version 9 (ICD-9) diagnostic and procedure codes, and the diagnosis related group (DRG) codes in the inpatient hospital files. Healthcare Common Procedure Coding System codes (HCPCS) and National Drug Codes (NDC) were used to identify systemic therapy administration in the outpatient, physician, durable medical equipment and Medicare Part D files using previously described methods.[21, 22]

1.2.4 Life expectancy

The primary health outcome was life expectancy, which was estimated from index diagnosis of stage IV NSCLC to date of death or censoring. We used information reported in the Medicare files on death dates from any cause, which were administratively censored for survival outcomes on 12/31/2011. At the end of follow up, only a small proportion of patients were censored, ranging from 2.1% in the BSC group to 6.7% in the target therapy treatment group. Survival time after the first year from diagnosis was discounted using a 3% annual rate.[23]

1.2.5 Costs

Our economic outcome of interest was lifetime spending. Total costs for each participant were calculated by summing the Medicare Part A, B and D reimbursements, primary insurance payments and patient-liability costs (deductibles and co-payments that are the patient's responsibility).[24] Costs were expressed in real terms, in 2013\$, by adjustment for general price inflation using the GDP Deflator, a measure of price inflation over time for all goods and services in the economy.[25] Costs incurred after one year from diagnosis were discounted using a 3% annual rate.[23]

1.2.6 Phases of care

Since costs of cancer care tend to exhibit a U shaped distribution over time (Appendix) and the entire cost histories are not observed for censored cases, we partitioned costs into three phases: initial, continuing, and terminal. This approach utilizes all information for participants who contribute data for a particular period. Thus, histories of long- and short-time survivors are represented in this calculation. The phase-specific approach can be used to estimate lifetime costs for incident cases that

are cumulative from date of diagnosis to death by combining phase-specific cost estimates with survival models when the entire cost history is not observed.[26]

The length of each phase was based on observed U-shaped patterns of costs over time (Appendix). Accordingly, we defined the duration of the initial phase as the month of diagnosis and the following 2 months. The terminal phase comprised the last 3 months of life, and the continuing phase as the remainder of the time and was therefore of variable duration. The initial phase captures the primary course of therapy. The continuing phase includes surveillance activities for detecting and treating recurrences. The terminal phase applies to care received at the end of life. Cost data were partitioned into 3-monthly intervals from diagnosis. A hierarchy was used to allocate the observation time to costing phases. Among patients who died, costs were first assigned to the terminal phase, then to the initial period, and any remaining time to the continuing period. Among censored patients, costs were assigned to the initial phase first then any costs incurred in the remaining time were categorized as the continuing phase.

1.2.7 Patient Characteristics

Characteristics expected to be related to treatment selection and some that may also potentially affect the outcomes of interest were identified for analytic strategies to reduce selection bias.[27] Socio-demographic and clinical characteristics included age, gender, race/ethnicity, marital status, US census tract level education and income, histology, presence of brain metastases, proxy indicator for acculturation using zip code level proportion of population who were born outside of the US, enrolment in Medicaid, and urban residence. Factors that may influence access to treatment included whether the patient was treated in a teaching hospital, census tract-level managed care

penetration, hospital bed and physician density (per 100,000 inhabitants), hospital referral region (HRR), and year of diagnosis. Hospital referral regions (HRR) were developed by Dartmouth Atlas of Health Care based on referral patterns to hospitals for Medicare patients. These regions represent areas with similar practice patterns.[28] There are 81 HRRs represented in the SEER regions in 2007. Patients were assigned to their HRR based on their residence zip code at the time of diagnosis of NSCLC. We calculated a comorbidity score that combines the conditions in the traditionally employed Charlson and Elixhauser indices using the method described by Gagne, et al.[29] We modified the score by excluding cancer conditions (Dr. Joshua Gagne, personal communication). The combined score has demonstrated a higher accuracy in predicting mortality in elderly patients using an external validation dataset compared to the individual indices. In addition, the combined score uses weights from more recent data and it reflects changes in prognosis of diseases stemming from improvements in medical care.[29] Each of the 18 conditions included in the combined score were further coded as indicator variables. Proxy measures of patient health and performance status at baseline included inpatient length of stay within one year prior to diagnosis, use of skilled nursing and home health care services, use of home oxygen and activities of daily living (ADL) aids (walkers, wheelchairs, hospital beds), as well as pre-diagnosis medical costs.[30] Claims starting from 12 months to 2 months prior to diagnosis were used for derivation of comorbidity scores, pre-diagnosis costs and indicators of functional status. The 2 months immediately prior to diagnosis were excluded to avoid including claims for treating symptoms of undiagnosed cancer.

1.2.8 Statistical Methods

Propensity Score Analysis

To balance observed baseline characteristics across treatment groups, we constructed a multinomial logistic regression model by regressing treatment (categorical variable with 3 levels: BSC, chemotherapy, and targeted therapy) on variables that potentially confound the treatment and outcome pathway and baseline covariates associated with treatment selection. The final model included 43 patient and provider characteristics. A weight representing the inverse of the predicted probability of treatment (IPW) from the multivariable logistic regression model was calculated for each patient. The conditional predicted probability of treatment is the propensity score (PS). We compared the distributions of these characteristics with and without applying IPW. To evaluate the quality of the PS weighting, we assessed the balance in baseline characteristics across treatment groups using standardized differences - the absolute difference in means divided by the pooled standard deviation. By convention, standardized differences of 10% or less are interpreted to signal a 'good' balance across groups.[27]

Life Expectancy

The estimation of life expectancy for the main analysis proceeded in two parts. First, an estimate of mean life expectancy was constructed based on the observed data (restricted mean). This was accomplished using a doubly robust estimation method which combines inverse probability weighting by propensity score with multivariate nonparametric Cox proportional hazard (PH) modeling of the relationship between covariates and survival for each treatment group. We checked the proportionality of

hazards assumption by comparing the log-cumulative hazard plots by treatment which confirmed that the PH assumption was not violated. Next, because the aim of the analysis was to estimate mean life expectancy over a lifetime horizon and since the observed survival curves did not reach a survival probability of zero (albeit, the extent of censoring was small, ranging from 2.1% in the BSC group to 6.7% in the target therapy treatment group), we opted to use parametric modeling to extrapolate survival beyond the observation period (extended means).[31, 32] First, we fit parametric models (Weibull, exponential, log-logistic, log-normal and gamma) to the IPW, adjusted survival curve for each treatment group. The Akaike's information criterion (AIC) test was used to select the model with the best fit.[32] However, even the best fitting model did not appear suitably to fit the IPW, adjusted survival curve. Hence, a more flexible parametric method was adopted.[31] Briefly, we fit piecewise exponential models to the IPW, adjusted survival curves for each treatment group (Appendix). Then we examined the kernel-smoothed hazard functions from the Cox PH models (Appendix). A long-term stable hazard trend was observed in all treatment groups when the survival probability reached 20% and lower. Using this cut point, the estimated hazard rates from the fitted piecewise-exponential models were averaged conditioning on treatment group. The tails of the IPW Cox PH model based survival function were fit using an exponential model with the rate parameter estimated using the average hazard rates from the piecewise exponential models for each treatment group to project survival beyond the observation period (Appendix).[33] Therefore, the extended mean life expectancy for each treatment group was based on a composite survival-function

estimator, using the IPW Cox PH based survival function and exponential parametric models beyond last follow up.

Phase-Specific Costs

We carried out a doubly robust estimation of phase-specific costs in which inverse-propensity weighting was combined with regression modeling with baseline covariates, including HRR fixed effects, and calendar year. We modeled phase-specific costs using generalized linear models (GLMs) with an Extended Estimating Equations (EEE) estimator.[34, 35] Briefly, the EEE model allows estimation of a flexible mean and variance function based on the data, which has been shown to reduce bias and increase efficiency compared to user specified parameters.[34] The semi-parametric EEE model can be implemented using the `pglm` command in STATA, which has been constructed by Basu.[35] This command simultaneously estimates the link and variance parameters from the data along with the regression parameters. All models were based on a doubly-robust estimator, with inclusion of IPW and baseline covariates. We used robust standard errors clustered at the patient level to account for correlation between cost observations for each patient. Post-estimation procedures were used to generate predicted costs. Both terminal and continuing phase costs depended on duration of survival, calendar year, and treatment group (Appendix). Several functional forms (e.g. main effects for time trends and survival length with and without interactions) were fit and models were selected based on goodness of fit tests: the Pearson correlation test, which tests the correlation between residuals and predicted costs on raw scale to determine systematic bias in prediction of costs; the Hosmer-Lemeshow test, which evaluates the calibration of predicted means across deciles with sample

means.[34, 36] The models with the best fit for the phase specific costs had a Pearson correlation coefficient ranging from -0.01 to 0.01, and no systematic patterns across deciles of predicted costs.

Lifetime cost estimation approach

We combined phase-specific cost predictions with survival curves to estimate lifetime costs using the Kaplan-Meier Sample Average (KMSA) estimator based on a previously proposed approach.[26, 37] Separate KMSA estimates were calculated for each treatment group. We calculated the sum of a weighted average of predicted 3-monthly costs over the 4-year period during which Medicare costs data was available. The KMSA estimator for expected total spending prior to censoring for costs (December 31, 2010) is:

$$E = \sum_{i=1} p_i * E_i$$

where: i =3-monthly intervals from diagnosis, range: 1 up to 16, $i=1$ represents the first 3 months of diagnosis, p_i = doubly robust, IPW Cox PH probability of surviving to period i using SEER-Medicare data, E_i = average modeled cost using EEE estimator incurred in period i among participants surviving to this time; costs for participants dying in period i are included; costs for participants who were censored in period i are excluded. This part of the KMSA estimator constitutes the restricted mean analysis since it does not include extrapolation of costs beyond the date of censoring, on December 31, 2010. The restricted mean approach was used in sensitivity analyses to examine the impact of modeling specifications on the outcome of interest.

Since restricted means would underestimate costs for patients who were alive after December 31, 2010, we relied on extrapolated cost predictions to estimate the extended mean lifetime spending. The KMSA estimator for extrapolated costs was calculated as follows:

$$E^* = \sum_j p_j^* * E_j^*$$

where: j =3-monthly period from diagnosis, range: 5 up to 26 (when <0.5% of patients remained alive), p_j = fitted survival probability based on the composite survival-function estimator, E_j^* = expected expenditure in period j , s.t.

$$E_j^* = d_j * \hat{t} + (1 - d_j) * \hat{c},$$

where: d_j = rate of dying in period j , \hat{t} = predicted average cost in terminal phase in period j , \hat{c} = predicted average cost in continuing phase in period j .

The KMSA estimator of expected total cumulative costs is:

$$E + E^*$$

This extended mean estimate of lifetime costs was used in the main analysis.

Cost Effectiveness Analysis

We calculated the incremental cost-effectiveness by first ranking the strategies in order of increasing effectiveness. Strategies that were strongly dominated, i.e., those that had a lower effectiveness and higher costs, were eliminated. Incremental cost

effectiveness ratios (ICERs) were calculated for each strategy in relation to the next best strategy. The ICER is a ratio of the difference in lifetime mean costs divided by the difference in mean life expectancy. Strategies with a higher ICER that were less effective than another strategy were eliminated by extended dominance. The ICERs were recalculated for the remaining strategies that were not eliminated by either strong or extended dominance.[38]

Subgroup analysis

To explore the value of first-line treatment with specific targeted therapies in the non-trial setting, we selected subgroups of patients who began targeted therapy treatment with first line bevacizumab combination therapy, erlotinib alone, or a doublet chemotherapy alone. The date of the first systemic therapy claim within 120 days from diagnosis was used to define the start date of first line treatment.[14] Cancer-directed treatments with dates within 29 days from initiation of therapy were flagged for the purpose of identifying combination therapies.[20] We estimated the extended means for life expectancy and costs for each group using methods described above. These estimates were adjusted for factors listed in Table 1.1 and discounted at 3% per annum.

Sensitivity Analyses

We conducted several sensitivity analyses of lifetime cost and life expectancy estimation using restricted means to evaluate the influence of model specification on these outcomes. These included IPW models with HRR fixed effects and IPW models without HRR fixed effects.

Instrumental Variable Methods

While PS methods can adjust for observed confounders that bias the treatment effect, these methods do not mitigate bias due to unobserved differences in known or unknown prognostic factors between the treated and untreated groups and across geographic areas. We investigated 1-year survival probability and costs to compare the consistency of results using PS analytic approaches and instrumental variable (IV) analyses. Consistent results across these analytic methods would signal that the causal effects were not influenced by omitted variables. The intuition behind IV methods is to compare groups not according to treatment they received, but rather according to the likelihood of receiving treatment, the instrument. The IV has to predict treatment choice but cannot be independently associated with the outcome, other than through its effect on treatment.[39] The IV can be regarded as a randomization mechanism, therefore, observed and unobserved characteristics should be similar across levels of the instrument. Area-level practice patterns are commonly used in IV approaches to adjust for selection bias in health services research.[40-42] This approach accounts for differences between patients across treatment groups, but it makes the assumption that potential confounders are randomly distributed across the geographic areas. We further account for possible unobserved confounding at the area level by including geographic area fixed effects. For example, this approach would account for the documented significant geographic variation in smoking patterns.[43] Smoking not only increases the risk of mortality in cancer patients, but is also correlated with predictors of treatment choice and response.[8, 44] To account for confounders both at the patient and area level, we used annual treatment rates within each HRR as the IV with fixed area effects to control for fixed unobserved differences between areas.

We first divided patients into quintiles according to annual rate of diffusion of targeted therapy in the HRR of residence, such that the number of patients in each quintile was approximately equal. We repeated the process for a second IV that estimated the annual rate of diffusion of chemotherapy treatment alone in each HRR. We constructed the instruments by calculating the rate of treatment by year within each HRR (chemotherapy or targeted therapy). We tested the relationship between each IV on each treatment type (chemotherapy and targeted therapy) using the F-test to assess whether each IV explained a significant portion of the variation in treatment choice. We also compared baseline characteristics by quintile of treatment diffusion for each IV separately to examine whether patients stratified according to rate of diffusion of each treatment type were similar in observed characteristics. Tests for trend were conducted across quintiles of adoption rates to assess whether patients were comparable across levels of each IV.

We adopted the two-stage least squares (2SLS) estimation approach for our IV-based sensitivity analysis. The outcomes considered for our sensitivity analysis were survival and cumulative costs at 1 year post diagnosis. In each stage, we included baseline covariates to control for residual differences between treatment groups and HRR fixed effects to control for area-level confounders. First, we estimated the probability of receiving targeted therapy as a function of baseline characteristics, HRR fixed effects and targeted therapy annual adoption rate at the HRR level. We repeated the prediction model for receipt of chemotherapy alone. In the second stage, we

included both predicted probabilities of treatment (of targeted therapy and of chemotherapy), baseline characteristics and HRR fixed effects as covariates to predict

1-year survival probabilities and cumulative costs by treatment group. We compared the IV-based predicted outcomes to IPW analyses and non-weighted analyses using the same set of covariates.

1.3 Results

1.3.1 Baseline Characteristics

A total of 10,285 patients met our eligibility criteria. Within this cohort, 3,191 (31%) received chemotherapy alone and for 1,834 (18%) patients treatment included a targeted therapy after diagnosis with Stage IV NSCLC. Among the targeted therapy group, 591 (32%), 1,119 (61%) and 112 (6%) of patients received erlotinib, bevacizumab, or both drugs (with and without chemotherapy), respectively, during their course of disease. Table 1.1 compares the patient, provider and area-level characteristics according to treatment group before and after weighting using the inverse probability of treatment (IPW, see a full list of covariates in Appendix). As expected, in the unweighted comparisons there was evidence of treatment selection bias. Patients who received any form of systemic therapy were more likely to be younger, married, have no comorbidities, and to be receiving care at a teaching hospital. Treated patients had fewer proxy indicators of poor PS at baseline (requiring home health care and skilled nursing services, ADL aids or hospitalization) and lower

Table 1.1. Baseline Characteristics.

Characteristic	BSC			Target			Chemo			Standardized Difference		
	Proportion											
	Unweighted			Inverse Probability of Treatment			Weighted			Standardized Difference		
Number of patients	5,260	1,834	3,191				5,260	1,834	3,191			
Age at diagnosis												
66-69	0.16	0.25	0.25	0.22 [†]	0.23 [‡]	0.01 [¶]	0.19	0.20	0.22	0.07 [†]	0.04 [‡]	0.03 [¶]
70-74	0.22	0.29	0.30	0.20	0.17	0.03	0.26	0.27	0.27	0.04	0.03	0.01
75-79	0.23	0.25	0.25	0.03	0.05	0.02	0.24	0.23	0.24	0.01	0.02	0.03
80-84	0.21	0.15	0.16	0.15	0.18	0.04	0.19	0.19	0.17	0.05	0.01	0.03
85+	0.18	0.06	0.05	0.43	0.38	0.06	0.13	0.11	0.10	0.10	0.04	0.05
Female gender	0.51	0.54	0.45	0.13	0.06	0.19	0.50	0.51	0.49	0.04	0.02	0.05
Race/ethnicity												
White	0.79	0.77	0.83	0.11	0.05	0.16	0.81	0.80	0.81	0.01	0.01	0.02
Black	0.10	0.06	0.08	0.07	0.15	0.08	0.08	0.07	0.09	0.02	0.02	0.04
Hispanic	0.04	0.05	0.04	0.03	0.02	0.05	0.04	0.05	0.04	0.02	0.03	0.05
Other	0.07	0.13	0.06	0.07	0.19	0.25	0.07	0.07	0.07	0.02	0.01	0.03
Marital status												
Single	0.09	0.09	0.07	0.06	0.00	0.07	0.08	0.08	0.08	0.01	0.01	0.02
Married	0.43	0.58	0.59	0.31	0.30	0.01	0.49	0.49	0.52	0.06	0.00	0.06
Other	0.48	0.33	0.35	0.28	0.31	0.02	0.43	0.42	0.40	0.06	0.01	0.05
Comorbidity score**												
0	0.58	0.67	0.67	0.20	0.20	0.00	0.61	0.62	0.63	0.04	0.01	0.03
1	0.17	0.16	0.16	0.03	0.03	0.01	0.17	0.17	0.17	0.00	0.01	0.01
2	0.09	0.09	0.07	0.07	0.02	0.04	0.09	0.10	0.08	0.03	0.04	0.07
3+	0.16	0.08	0.09	0.20	0.25	0.05	0.13	0.12	0.12	0.04	0.04	0.00
COPD prior to diagnosis	0.25	0.21	0.22	0.07	0.11	0.04	0.24	0.24	0.23	0.02	0.01	0.02
Brain metastases	0.22	0.12	0.18	0.10	0.28	0.18	0.19	0.19	0.18	0.02	0.02	0.01
Histology												
Large cell	0.05	0.04	0.05	0.02	0.05	0.07	0.05	0.04	0.05	0.01	0.01	0.02
Adenocarcinoma	0.56	0.64	0.52	0.07	0.18	0.25	0.55	0.56	0.56	0.01	0.02	0.01
BAC	0.01	0.03	0.01	0.02	0.12	0.14	0.02	0.02	0.02	0.01	0.02	0.02
NOS	0.38	0.29	0.42	0.07	0.20	0.27	0.38	0.38	0.38	0.01	0.01	0.00
Long-term care	0.15	0.07	0.08	0.24	0.27	0.03	0.12	0.11	0.11	0.04	0.03	0.01
Skilled nursing services	0.09	0.02	0.03	0.28	0.29	0.02	0.06	0.05	0.04	0.11	0.04	0.08
Home oxygen	0.19	0.13	0.16	0.08	0.16	0.08	0.17	0.16	0.17	0.00	0.03	0.03
ADL aids	0.12	0.08	0.06	0.20	0.14	0.06	0.10	0.09	0.09	0.05	0.05	0.00
Medicaid enrollment	0.22	0.21	0.12	0.27	0.01	0.25	0.19	0.18	0.16	0.07	0.01	0.06
Urban residence	0.90	0.91	0.90	0.02	0.02	0.04	0.90	0.90	0.90	0.00	0.01	0.00
Teaching hospital	0.00	0.17	0.26	0.84	0.64	0.23	0.00	0.12	0.12	0.52	0.51	0.01
College education ***												
1(low)	0.21	0.16	0.19	0.04	0.13	0.09	0.20	0.20	0.20	0.00	0.00	0.00
2	0.20	0.20	0.19	0.03	0.01	0.02	0.21	0.19	0.20	0.02	0.04	0.02
3	0.19	0.19	0.21	0.04	0.01	0.05	0.20	0.20	0.20	0.01	0.00	0.01
4	0.21	0.19	0.21	0.01	0.02	0.04	0.20	0.21	0.21	0.00	0.01	0.00
5 (high)	0.19	0.26	0.19	0.01	0.16	0.15	0.19	0.20	0.20	0.01	0.03	0.02
Income***												
1 (low)	0.21	0.16	0.19	0.06	0.14	0.07	0.20	0.19	0.20	0.01	0.02	0.01
2	0.20	0.19	0.19	0.03	0.04	0.01	0.20	0.20	0.20	0.02	0.00	0.01
3	0.20	0.20	0.20	0.01	0.01	0.00	0.20	0.20	0.20	0.00	0.00	0.00
4	0.20	0.20	0.20	0.00	0.00	0.00	0.20	0.20	0.20	0.01	0.01	0.00
5 (high)	0.18	0.25	0.21	0.08	0.16	0.08	0.19	0.20	0.21	0.04	0.03	0.01

Table 1.1. (Continued)

*Other covariates included in PS estimation: Alcohol abuse, Cardiac arrhythmias, CHF, Chronic

Characteristic	BSC Target Chemo			Standardized Difference			BSC Target Chemo			Standardized Difference		
	Proportion			Standardized Difference			Proportion			Standardized Difference		
	Unweighted			Standardized Difference			Inverse Probability of Treatment Weighted			Standardized Difference		
Prior year costs												
(quintile)												
1 (low)	0.21	0.17	0.20	0.03	0.11	0.08	0.20	0.19	0.20	0.00	0.03	0.02
2	0.18	0.22	0.22	0.09	0.10	0.01	0.19	0.20	0.20	0.02	0.02	0.00
3	0.18	0.23	0.21	0.07	0.11	0.04	0.20	0.21	0.20	0.01	0.02	0.01
4	0.18	0.23	0.21	0.07	0.13	0.06	0.20	0.19	0.20	0.02	0.03	0.04
5 (high)	0.24	0.15	0.16	0.20	0.24	0.04	0.21	0.21	0.19	0.04	0.01	0.06
Year of diagnosis												
2007	0.34	0.34	0.34	0.01	0.00	0.01	0.34	0.33	0.34	0.01	0.02	0.01
2008	0.34	0.32	0.34	0.01	0.05	0.05	0.34	0.34	0.34	0.01	0.01	0.00
2009	0.32	0.34	0.32	0.00	0.04	0.04	0.32	0.33	0.32	0.00	0.02	0.01

pulmonary disease, Coagulopathy, Complicated diabetes, Deficiency anemias, Dementia, Fluid and electrolyte disorder, HIV/AIDS, Hemiplegia, Hypertension, Liver disease, PVD, Psychosis, Pulmonary circulation disorder, Renal failure, Weight loss, hospital days for COPD prior to cancer diagnosis, census tract level hospital bed and physician density, managed care penetration, proportion foreign born, hospital length of stay within a year prior to cancer diagnosis, hospital referral region not shown (see Appendix) **determined using Charlson and Elixhauser combined score †chemotherapy vs. BSC ‡targeted therapy vs. BSC ¶targeted therapy vs. chemotherapy *** census tract quintile

medical costs prior to diagnosis. Patients treated with targeted therapy compared to chemotherapy alone were more likely to be female, non-Hispanic, non-white, or non-black, have a histopathologic diagnosis of adenocarcinoma and Medicaid co-insurance, live in areas with high managed care penetration, and areas with a highly educated and foreign born population. Compared to the chemotherapy alone treatment group, those treated with targeted therapy were less likely to have brain metastases or to be treated at a teaching hospital. In the IPW analyses, the balance in the baseline characteristics across the treatment groups improved considerably. All standardized differences were notably smaller than 10% with the exception of a higher proportion of systemic therapy patients who were managed at a teaching hospital compared to the BSC group.

1.3.2 Life Expectancy

Patients who were ever exposed to cancer-directed treatment during their course of disease with Stage IV lung cancer had a longer survival compared to those managed with BSC. Based on undiscounted survival time and doubly robust, IPW Cox PH models, the median overall survival estimates were 2.4 (IQR, 1.3-5.2), 6.5 (IQR, 3.3-13.1), and 9.8 (IQR, 4.7-17.2) months in the BSC, chemotherapy and targeted therapy groups, respectively. Surprisingly, our subgroup analysis based on first-line therapy exposure, revealed that the adjusted median survival for patients selected for first line erlotinib therapy in routine care was only marginally longer compared to a counterfactual group of patients managed with BSC, 4.7 (IQR, 2.7-11.5) months vs. 2.6 (IQR, 1.3-5.5) months. A much longer median adjusted OS was observed for those treated with first line doublet chemotherapy, 8.1 months (IQR, 4.1-15.5), and for patients who initiated combination therapy with bevacizumab, 10.5 months (IQR, 5.6-18.3).

Discounted mean life expectancy and lifetime costs adjusted for inflation (2013 \$) are shown in Tables 1.2 and 1.3 by treatment 'ever' category and for first-line treatment subgroups, respectively. These lifetime estimates are based on IPW, doubly-robust analyses and projections beyond last censored observation. The largest discounted mean life expectancy improvement, of 5.4 months, was seen in patients ever treated with chemotherapy alone relative to those managed with BSC (Table 1.2). Patients who received targeted therapy at some point, lived on average 2.4 months longer compared to cases treated with chemotherapy alone (Table 1.2). Based on first-line therapy subgroup analyses (Table 1.3), the mean life expectancy increased by only 1.2 months for treatments that combined bevacizumab with a chemotherapy doublet vs.

chemotherapy alone. The mean survival associated with first line erlotinib therapy was substantially shorter compared to treatment with a chemotherapy doublet, 8.5 vs. 12.2 months.

Table 1.2. Cost Effectiveness Analysis Results by Treatment Category ‘Ever’.

Treatment*	Mean Lifetime Cost [†]	Cost Difference	Mean Life Expectancy [†] (months)	Mean Life Expectancy (years)	Change in Life Expectancy (years)	ICER [‡] (\$/LY)
BSC[¶]	\$45,556		5.28	0.44		
Any Chemotherapy	\$86,039	\$40,483	10.66	0.89	0.45	90,297
Targeted	\$125,119	\$39,080	13.02	1.16	0.20	198,712

Table 1.3. Cost Effectiveness Analysis Results by First-Line Therapy.

Treatment**	Mean Lifetime Cost [†]	Cost Difference	Mean Life Expectancy [†] (months)	Mean Life Expectancy (years)	Change in Life Expectancy (years)	ICER (\$/LY)
BSC[¶]	\$47,902		5.17	0.43		
Erlotinib	\$83,732	dominated	8.51	0.71	dominated	dominated
Doublet Chemotherapy	\$95,154	\$47,252	12.21	1.02	0.59	80,543
Bevacizumab	\$149,987	\$54,833	13.43	1.12	0.10	548,330

*patients grouped into treatment categories based on receipt of treatment anytime after diagnosis; based on projected costs and survival beyond last observed data (extended means)

† based on doubly robust estimators (inverse probability weighting by propensity score and multivariate outcome regression models); models were adjusted for age, race, gender, marital status, comorbidity score, individual comorbidities, histology, brain metastases, enrollment in Medicaid, urban residence, hospital teaching status, pre-diagnosis costs, indicators of functional status prior to diagnosis (skilled nursing, long-term care, hospital stays, use of home oxygen, ADL aids), census level college education, income, physician density, hospital bed density, managed care penetration, proxy indicator for acculturation (proportion foreign born), year of diagnosis, and hospital referral region

‡ICER=incremental cost effectiveness ratio, ratio of difference in mean lifetime costs (2013 \$) to mean life years ; after 1 year, costs and survival length discounted by 3% per annum

¶BSC=best supportive care

**patients grouped into treatment categories based on first-line therapy initiation within 120 days from diagnosis

1.3.3 Costs

On average, the discounted cost of medical management with BSC over a lifetime was \$45,600 (2013 US\$). The corresponding lifetime cost estimates for the chemotherapy and targeted therapy groups were \$86,000 and \$125,100, respectively, or approximately \$40,000 more for each technological advance (Table 1.2).

Patients who initiated therapy with a bevacizumab-based combination treatment, had the highest lifetime costs of around \$150,000 (Table 1.3). Costs for those who were treated with first-line chemotherapy were approximately \$55,000 lower over a lifetime compared to the first-line bevacizumab group.

We also decomposed the cumulative medical expenditures by service type and into monthly spending by phase of care (Table 1.4 and 1.5). First, we carried out a comparison of mean IPW monthly costs by phase of care between the BSC patients and each of the treatment groups *prior to* initiation of therapy to examine whether residual unobserved confounders may explain the differences in cumulative and monthly costs. These analyses revealed no significant differences in monthly costs (data not shown), bolstering the case that group differences in cumulative and monthly costs arose from survival differences and treatment-related management.

The decomposed estimates revealed that systemic therapy costs account for the largest proportion of medical care costs. In the targeted therapy group, a quarter of the overall spending, or \$32,300, was attributable to costs related to targeted treatments, and another 20% of total costs, approximately \$25,000, was spent on chemotherapy (drug costs and administration costs). Similarly, in the chemotherapy treatment only group, drug related costs accounted for a substantial proportion (22.0%) of the total expenditures (Table 1.4).

Table 1.4. Costs by Category of Spending and Treatment (2013 \$).

Treatment*	Durable Medical Equipment		Home Health Agency		Hospice		Inpatient Hospital		Physician		Outpatient		Chemotherapy		Target Therapy		Total Cost
BSC	\$588	1.3% †	\$946	2.1%	\$4,485	9.8%	\$25,654	56.3%	\$9,561	21.0%	\$4,322	9.5%	\$0	0.0%	\$0	0.0%	\$45,556
Chemo	\$1,215	1.4%	\$2,349	2.7%	\$3,900	4.5%	\$32,137	37.4%	\$18,152	21.1%	\$9,358	10.9%	\$18,928	22.0%	\$0	0.0%	\$86,039
Targeted	\$868	0.7%	\$2,322	1.9%	\$3,815	3.0%	\$31,622	25.3%	\$19,490	15.6%	\$9,797	7.8%	\$24,912	19.9%	\$32,293	25.8%	\$125,119

* using Kaplan-Meier Sample Average (KMSA) cost estimator based on doubly robust, inverse probability of treatment weighted (IPW) monthly costs and survival probabilities ; propensity of receiving a treatment was estimated using multinomial logistic regression model with the following covariates: age, race, gender, marital status, comorbidity score, individual comorbidities, histology, brain metastases, enrollment in Medicaid, urban residence, hospital teaching status, pre-diagnosis costs, indicators of functional status prior to diagnosis (skilled nursing, long-term care, hospital stays, use of home oxygen, ADL aids), census level college education, income, physician density, hospital bed density, managed care penetration, proxy indicator for acculturation (proportion foreign born), year of diagnosis, and hospital referral region; after 1 year, costs discounted by 3% per annum
 †percent of total cost

The terminal phase was the most resource intensive period. Although the monthly terminal costs were comparable across all treatment groups, it is noteworthy that the pattern of spending did differ across the groups (Table 1.5). For example, patients in the BSC group had significantly higher inpatient hospital monthly costs compared to patients treated with systemic therapy. Interestingly, a large amount of spending in the terminal phase continued to be allocated towards drug therapy for patients who received any form of systemic therapy (Table 1.5). For example, in the targeted therapy group, 20% of terminal phase costs were attributable to drug therapy and a mean of \$1,492 per month was spent on targeted therapy alone.

The initial phase of treatment was also associated with high mean monthly total costs (Table 1.5). Almost 20% and 40% of the costs in the initial phase were comprised of drug therapy spending in the chemotherapy and targeted therapy groups, respectively. The continuing phase was the least costly (total monthly cost range: \$3,392 - \$7,573), but net of drug costs, the monthly costs in this phase did not differ by treatment group.

1.3.4 Cost-Effectiveness Analysis

For strategies based on treatment exposure ever, the incremental cost effectiveness ratios (ICERs) using a lifetime horizon were \$90,300 per year of life and \$198,700 per life-year for chemotherapy vs. BSC and targeted therapy vs. chemotherapy respectively (Table 1.2).

In our subgroup analysis which compared groups according to first-line therapy, the erlotinib strategy was eliminated by extended dominance since the ICER associated with this treatment was higher compared to the ICER for first-line chemotherapy.

Table 1.5. Monthly Costs by Phase of Care and Treatment (2013 \$).

Treatment*	Phase	Total Costs	Costs without Drug Therapy	Inpatient Hospital Costs	Outpatient Costs	Physician Costs	Hospice Costs	Home Health Care Costs	Durable Medical Equipment Costs	Chemotherapy Costs	Targeted Therapy Costs
Mean (95% CI) 2013 US \$											
Targeted Therapy	Initial	11,874 (11,460-12,288)	7,247 (6,877-7,617)	3,359 (3,066-3,651)	1,323 (1,235-1,411)	2,308 (2,194-2,422)	14 (1-26)	147 (122-171)	97 (78-116)	1,902 (1,724-2,080)	2,726 (2,542-2,909)
	Continuing	7,573 (7,245-7,901)	2,927 (2,750-3,105)	907 (804-1,011)	583 (535-631)	1,080 (1,020-1,141)	125 (78-171)	149 (123-175)	79 (63-96)	2,058 (1,867-2,249)	2,587 (2,396-2,779)
	Terminal	12,015 (11,400-12,630)	9,619 (9,041-10,198)	5,575 (5,081-6,070)	761 (573-948)	1,717 (1,615-1,819)	1,065 (958-1,171)	389 (334-444)	113 (99-127)	903 (797-1,009)	1,492 (1,362-1,623)
Chemotherapy	Initial	10,168 (9,847-10,490)	8,329 (8,009-8,650)	3,820 (3,553-4,087)	1,555 (1,481-1,629)	2,717 (2,622-2,811)	11 (5-17)	143 (120-166)	84 (76-93)	1,839 (1,745-1,933)	
	Continuing	5,139 (4,897-5,381)	3,190 (2,992-3,389)	1,169 (1,032-1,305)	594 (554-634)	1,084 (1,014-1,154)	122 (89-154)	143 (123-163)	82 (71-94)	1,949 (1,812-2,086)	n/a
	Terminal	11,850 (11,444-12,257)	10,685 (10,283-11,088)	6,351 (5,993-6,708)	785 (736-835)	2,046 (1,958-2,133)	1,034 (961-1,107)	360 (329-390)	110 (101-119)	1,165 (1,090-1,240)	
BSC	Initial	8,493 (8,074-8,913)	8,493 (8,074-8,913)	4,759 (4,412-5,106)	1,192 (1,040-1,345)	2,079 (1,984-2,174)	222 (188-256)	158 (138-178)	83 (73-93)		
	Continuing	3,392 (3,106-3,678)	3,392 (3,106-3,678)	1,027 (863-1,191)	636 (542-730)	1,071 (912-1,230)	420 (334-505)	123 (101-144)	81 (67-94)	n/a	n/a
	Terminal	12,711 (12,351-13,071)	12,711 (12,351-13,071)	8,203 (7,876-8,531)	633 (597-668)	2,049 (1,984-2,115)	1,469 (1,409-1,529)	261 (243-280)	90 (83-97)		

*estimates based on inverse probability of treatment weighted (IPW) monthly costs; propensity of receiving a treatment was estimated using multinomial logistic regression model with the following covariates: age, race, gender, marital status, comorbidity score, individual comorbidities, histology, brain metastases, enrollment in Medicaid, urban residence, hospital teaching status, pre-diagnosis costs, indicators of functional status prior to diagnosis (skilled nursing, long-term care, hospital stays, use of home oxygen, ADL aids), census level college education, income, physician density, hospital bed density, managed care penetration, proxy indicator for acculturation (proportion foreign born), year of diagnosis, and hospital referral region

The first-line chemotherapy strategy compared to BSC yielded an ICER of \$80,500 per additional life year (Table 1.3). Relative to first-line chemotherapy, the addition of bevacizumab to first-line therapy resulted in a cost of almost \$550,000 per life year gained (Table 1.3).

1.3.5 Sensitivity Analyses

We conducted several sensitivity analyses to test the effects of modeling assumptions and potential omitted variable bias on our results. In table 1.6, we present the results of several modeling approaches that were done using restricted mean outcomes (without extrapolation beyond observed period). Not accounting for selection bias based on observed confounders resulted in a more favorable ICER for chemotherapy, at around \$85,000 per year of life, and for targeted therapy, at \$160,000 per year of life, compared to the next best strategy. Our base case analysis, IPW multivariate models adjusted for residual confounding including fixed HRR effects, produced an ICER for targeted therapy in mid-range of other modeling approaches, \$91,700 and \$184,400 per life year for chemotherapy and targeted therapy, respectively. Without the doubly-robust estimation, IPW weighted analyses with HRR fixed effects yielded slightly lower ICERs and those without HRR fixed effects produced a higher ICER for targeted therapy. These results suggest some residual confounding by baseline characteristics and HRR residence, albeit to a small extent, compared to analyses that were based on IPW estimation alone.

Table 1.6. Sensitivity Analyses.

Models	Treatment	Mean Cost	Cost Difference	Mean Life Expectancy (months)	Mean Life Expectancy (years)	Change in Life Expectancy (years)	ICER [†] (\$/LY gained)
Unadjusted	BSC [‡]	\$45,391		5.10	0.43		
	Chemotherapy	\$89,456	\$44,065	11.35	0.95	0.52	84,740
	Target Therapy	\$142,233	\$52,777	15.32	1.28	0.33	159,930
Doubly robust^{**},¶	BSC	\$45,410		5.24	0.44		
	Chemotherapy	\$85,355	\$39,945	10.47	0.87	0.44	91,652
	Target Therapy	\$124,377	\$39,022	13.01	1.08	0.21	184,356
IPW with HRR fixed effects^{**},††	BSC	\$45,865		5.40	0.45		
	Chemotherapy	\$85,328	\$39,463	10.95	0.91	0.46	85,789
	Target Therapy	\$126,445	\$41,117	13.77	1.15	0.24	171,321
IPW without HRR fixed effects^{¶¶},‡‡	BSC	\$46,080		5.44	0.45		
	Chemotherapy	\$87,507	\$41,427	11.21	0.93	0.48	86,306
	Target Therapy	\$130,735	\$43,228	13.79	1.15	0.22	196,491

*based on observed data (restricted means)

† ICER=incremental cost effectiveness ratio, ratio of difference in mean lifetime costs (2013 \$) to mean life years ; after 1 year, costs and survival length discounted by 3% per annum

‡BSC=best supportive care

¶based on doubly robust estimators (inverse probability weighting by propensity score and multivariate outcome regression models); models were adjusted for age, race, gender, marital status, comorbidity score, individual comorbidities, histology, brain metastases, enrollment in Medicaid, urban residence, hospital teaching status, pre-diagnosis costs, indicators of functional status prior to diagnosis (skilled nursing, long-term care, hospital stays, use of home oxygen, ADL aids), census level college education, income, physician density, hospital bed density, managed care penetration, proxy indicator for acculturation (proportion foreign born), year of diagnosis, and hospital referral region fixed effects

**propensity of receiving a treatment was estimated using multinomial logistic regression model with the following covariates: age, race, gender, marital status, comorbidity score, individual comorbidities, histology, brain metastases, enrollment in Medicaid, urban residence, hospital teaching status, pre-diagnosis costs, indicators of functional status prior to diagnosis (skilled nursing, long-term care, hospital stays, use of home oxygen, ADL aids), census level college education, income, physician density, hospital bed density, managed care penetration, proxy indicator for acculturation (proportion foreign born), year of diagnosis, and hospital referral region

†† Kaplan-Meier Sample Average (KMSA) included estimates from models with inverse probability of treatment weights (IPW) and HRR fixed effects

‡‡ Kaplan-Meier Sample Average (KMSA) included estimates from models with inverse probability of treatment weights (IPW)

¶¶propensity of receiving a treatment was estimated using multinomial logistic regression model with the following covariates: age, race, gender, marital status, comorbidity score, individual comorbidities, histology, brain metastases, enrollment in Medicaid, urban residence, hospital teaching status, pre-diagnosis costs, indicators of functional status prior to diagnosis (skilled nursing, long-term care, hospital stays, use of home oxygen, ADL aids), census level college education, income, physician density, hospital bed density, managed care penetration, proxy indicator for acculturation (proportion foreign born), and year of diagnosis

1.3.6 Instrumental Variable Analysis

The instruments using HRR-by-year rates of the adoption of targeted therapy and chemotherapy significantly predicted the likelihood of lung cancer treatment choices ($F = 147$ and 125 , p -value $< .001$, respectively for targeted therapy and chemotherapy). The likelihood of receiving treatment was significantly associated with the quintile of the instruments - chemotherapy receipt increased from 17.8% to 45.0% and targeted therapy ranged from 6.3% to 30.5% from the lowest quintile to the highest quintile of the instruments. Patient characteristics according to the lowest and highest quintile of each instrument were reasonably balanced across the quintiles of the instruments (see Appendix). Residual differences were controlled for in the doubly-robust estimation. The instrumental variable analyses indicated that the incremental 6-month and 12-month differences between strategies in overall survival and cumulative costs were not significantly different from differences estimated by the doubly-robust IPW approach.

1.4 Discussion

We performed a cost-effectiveness analysis of targeted therapies outside the clinical trial setting in a population-based study of elderly patients with Stage IV NSCLC. Our results indicate that targeted therapy given in routine care generates a modest survival benefit compared to chemotherapy alone. Unlike most cost-effectiveness analyses, which are based on decision analytic models with efficacy inputs from selected clinical trial participants, we based our study on the real-world setting to reflect effectiveness and expenditure outcomes using contemporary practice patterns. Our

results suggest that the incremental cost-effectiveness ratio for targeted therapy of \$198,700 per additional life year exceeds the WHO acceptable willingness to pay threshold for a cost-effective intervention of \$150,000 per life year.[45] In a subgroup analysis, we found that initiation of bevacizumab in combination with chemotherapy yielded an ICER of almost \$550,000 per life-year. First-line erlotinib therapy was a dominated strategy since it resulted in an ICER that was higher than that for first-line doublet chemotherapy, yet its effectiveness in terms of life expectancy was lower, 8.5 months vs. 12.2 months, respectively.

Our results for first-line bevacizumab-based therapy are consistent in value with an economic analysis which used efficacy outcomes from the landmark trial (ECOG 4599) comparing carboplatin and paclitaxel with and without bevacizumab that yielded an ICER of \$309,000 per life year from the US payer perspective.[18, 46] Both, our observational study and the trial-based cost-effectiveness analysis suggest that bevacizumab treatment is associated with a low economic value. The survival outcomes observed in our study among patients who were treated with bevacizumab in the first line setting were comparable to those reported by Zhu, et al.[14] In that observational study of patients aged 65 years or older, the median OS for bevacizumab in combination with carboplatin and paclitaxel was 9.7 months and the 1-year survival probability was 39.6%, outcomes that were not significantly different from carboplatin and paclitaxel combination therapy alone. More careful selection of patients in a trial setting yielded results for overall survival that ranged from non-significant to a 2-month significant benefit in the ECOG 4599 trial for bevacizumab combination therapy compared to chemotherapy alone.[11, 47, 48] In contrast to the known predictive

biomarkers which correlate with response to erlotinib, factors predictive of response or toxicity with bevacizumab in non-squamous cell tumors are yet to be elucidated.[49] Future research should focus on identifying predictive markers to guide bevacizumab therapy towards subgroups of patients who are more likely to benefit from addition of bevacizumab to first-line chemotherapy.

Our finding of a surprisingly low adjusted median OS of 4.7 months for patients selected for first line erlotinib therapy in routine care compared to a counterfactual group of patients treated with first line doublet chemotherapy of 8.1 months warrants a closer examination of treatment prescribing patterns. In a companion observational analysis of elderly lung cancer patients, we found that only 5.2% of Stage IV non-squamous NSCLC patients had a claim for a molecular test prior to initiation of first-line therapy.(ref 3rd paper) This finding is corroborated by another study which also reported that biomarker screening is underutilized in routine care. In that study, only 12% of US acute-care hospitals ordered the EGFR assay in 2010, which represented 5.7% of guideline-directed patients.[9] Yet, outcomes with erlotinib therapy are correlated with EGFR mutation status and therefore dependent on molecular testing. While unselected patients with advanced NSCLC have response rates of 8% to 9% and median progression-free survival (PFS) of 3.4 months with erlotinib, those whose tumors harbour drug sensitizing EGFR mutations have response rates of 68% and median PFS of 12 months on erlotinib.[8] In a recent trial of first line erlotinib therapy in patients with tumors positive for the EGFR drug sensitizing mutations, median overall survival was 19.3 months.[7] The lower median OS found in our observational cohort compared to the results in that trial may be due, in part, to differences in age and functional status.

Still, a three-fold difference in median OS, coupled with the low proportion of patients with evidence of molecular testing suggest that molecularly guided therapy is underutilized in routine practice. One way to optimize the value of erlotinib therapy is to condition its use on EGFR positive status. Commercial EGFR mutation assays were first marketed in 2005 and many laboratory-developed tests (LDTs) for EGFR mutations are available, providing ready access to EGFR testing.[9] In addition, ascertainment of predictive biomarker status prior to selection of TKI therapy in *all* patients with non-squamous, advanced stage NSCLC has been endorsed by professional societies including the American Society for Clinical Oncology (ASCO), the College of American Pathologists (CAP), the International Association for the Study of Lung Cancer (IASLC), the Association for Molecular Pathology (AMP), as well as NCCN.[8, 50, 51]

Evidence suggests that better value for EGFR TKIs, in terms of return on medical spending, is achievable through universal molecular testing of guideline-recommended patients. Handorf et al. conducted a cost effectiveness analysis of EGFR mutation testing to inform first-line treatment in patients with stage IV NSCLC in the United States. Compared to standard of care with carboplatin and paclitaxel combination chemotherapy, testing followed by erlotinib treatment in EGFR mutation positive tumors, or chemotherapy in wild type tumors yielded ICERs in the range of \$110,600 to \$122,200 per QALY. Compared with carboplatin, pemetrexed and bevacizumab as the standard of care, the testing strategy had ICERs of \$25,500 to \$44,000 per QALY.[17] In a separate analysis, we also found that EGFR mutation and anaplastic lymphoma kinase (ALK) rearrangement guided therapy in non-squamous, Stage IV NSCLC patients yields good value with an ICER of \$150,000 per QALY compared to cisplatin-

pemetrexed treatment in unselected patients.(ref 1st paper) The effect of EGFR mutation guided therapy on the health care budget appears to have a small impact. In a plan of 500,000 members, the budget impact did not exceed \$0.019 per member per month in one analysis.[52] Taken as a whole, the return on medical spending for erlotinib would be improved by better targeting of patients most likely to benefit from this TKI through molecular testing.

The limitations of our study need to be considered in the interpretation of our findings. We relied on observational data in our analysis, which is subject to selection biases. We mitigated the imbalance between treatment groups with the use of doubly robust methods, which included propensity score estimation with 43 potential confounders of treatment selection and outcomes. We included proxy indicators of known predictors of therapy choice, such as performance status, and smoking history, as well as phenotypic characteristics that have been shown to correlate with EGFR drug sensitizing mutations.[8, 30] We further adjusted for residual confounding and unobserved area-level confounders by using a doubly robust estimator, including fixed HRR effects. Still, propensity score methods will estimate a causal effect that is unbiased to the extent that there are no omitted variables which confound the relationship between treatment and the outcome. To account for potential omitted variable bias, in our sensitivity analyses, we conducted instrumental variable analyses. All results yielded consistent findings.

From an external validity standpoint, the results of our analysis are generalizable to most elderly patients (65 years of age and older) who are managed in the community setting. The SEER population is generally representative of the US population.[53]

The median age of NSCLC patients at diagnosis is 71 years and two thirds of NSCLC patients are 65 or older at the time of diagnosis.[54] In addition, our analysis is based mainly on patients who were not enrolled in a clinical trial, thus the results are generalizable to the majority of patients afflicted by this disease. However, our analysis does not reflect treatment patterns and costs in managed care populations, who have been shown to differ systematically from FFS beneficiaries.[55] Furthermore, the results are restricted to direct medical costs and thus do not include time costs, or costs due to lost productivity. These metrics were outside the scope of the present analysis.

In an era of a growing cost burden of cancer care, the cost of targeted therapies has come under increased scrutiny mostly as a response to the sticker shock from drug prices.[3-5, 16, 56] Based on treatment patterns in routine care, the economic value generated by targeted therapies in the setting of advanced NSCLC is unfavorable relative to conventional benchmarks. Improvements in cost-effectiveness may be possible using predictive molecular marker testing to identify patients with drug sensitizing mutations that predispose to a favorable response to therapy. Future policy efforts aimed at incentivizing molecularly guided therapy should be evaluated towards broader implementation of screening for genetic markers. Such policies may include value-based benefit designs that reduce patient cost-sharing with accompanying evidence of positive results for EGFR drug sensitizing mutations, or reference pricing whereby reimbursement level for targeted therapies to providers is made contingent on the evidence base, or guideline recommendations (e.g., with higher reimbursement in cases of guideline-concordant care).

1.5 Appendix

Figure 1.A.1. Hazard functions by treatment group. The vertical lines correspond to the cut-point on the K-M survival curve where probability of survival is 20% or less.

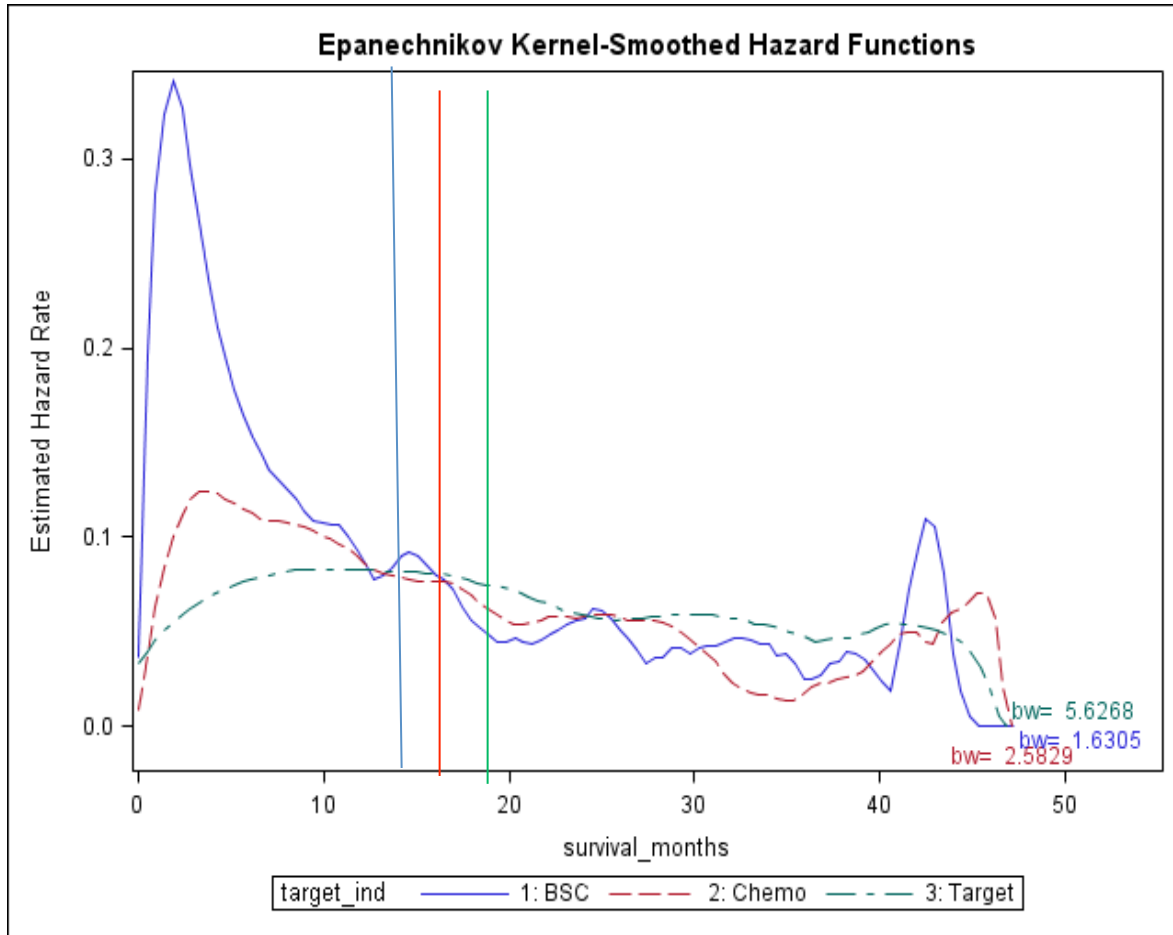


Figure 1.A.2. Doubly robust survival curves and piecewise exponential model calibration.

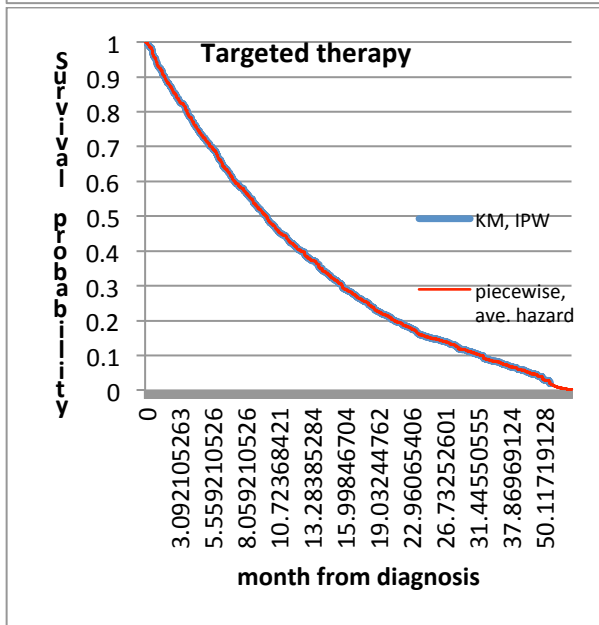
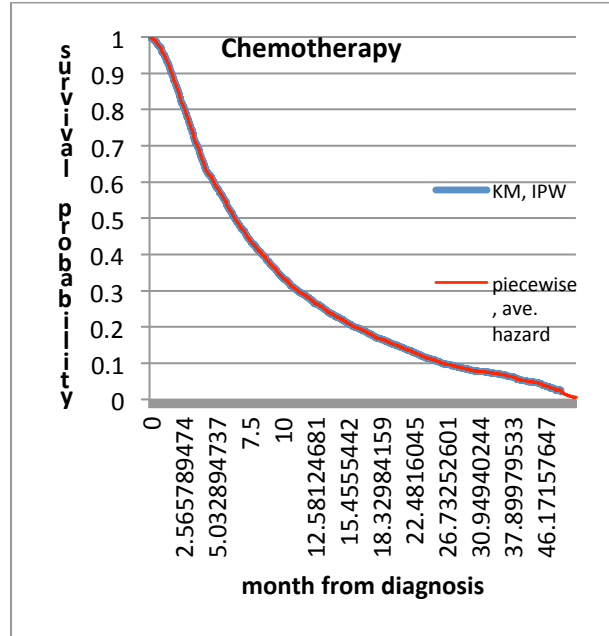
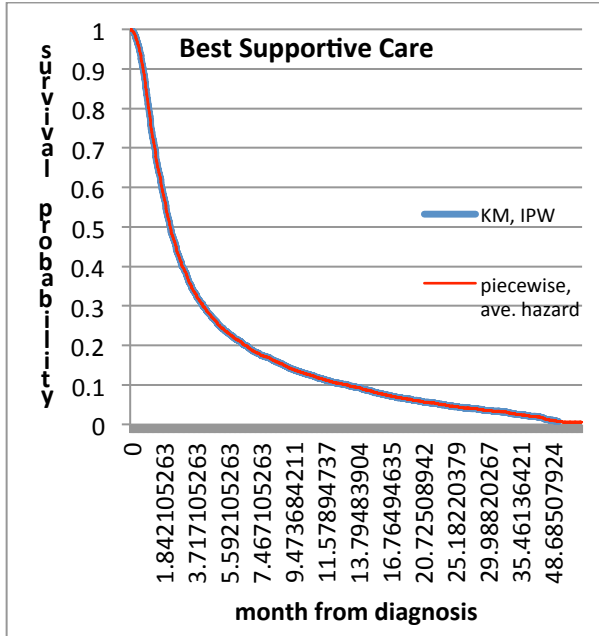


Table 1.A.1. Predicted Survival According to Treatment for Unadjusted, Doubly-Robust and Instrumental Variable Results.

	OLS	Delta (95% CI)	IPW, doubly robust, HRR fixed effects	Delta (95% CI)	IPW, doubly robust, HSA fixed effects	Delta (95% CI)	Original HRRs for local area treatment pattern IV 2SLS - XTIVREG code	Delta (95% CI)	Original HSAs for local area treatment pattern IV 2SLS - XTIVREG code	Delta (95% CI)
Predicted 6-month survival										
BSC	0.223		.226		.225		.201		.195	
Chemotherapy	0.535	.312 (.290, .334)	.528	.302 (.277, .327)	.528	.303 (.278, .328)	.495	.294 (.077, .512)	.548	.353 (.189, .517)
Targeted	0.701	.166 (.140, .192)	.680	.152 (.119, .185)	.681	.153 (.120, .186)	.832	.337 (.130, .544)	.765	.217 (.040, .394)
Predicted 12-month survival										
BSC	.113		.112		.112		.092		.083	
Chemotherapy	.291	.178 (.158, .197)	.284	.172 (.150, .194)	.283	.171 (.150, .193)	.264	.172 (-.022, .367)	.293	.210 (.064, .358)
Targeted	.432	.141 (.118, .164)	.418	.134 (.102, .166)	.418	.135 (.103, .168)	.541	.277 (.092, .462)	.515	.222 (.063, .380)

Table 1.A.2. Predicted Costs According to Treatment for Unadjusted, Doubly-Robust and Instrumental Variable Results.

Mean Predicted 6-month cost	OLS	Delta (95% CI)	IPW, doubly robust, OLS, HRR fixed effects	Delta (95% CI)	IPW, doubly robust, OLS, HSA fixed effects	Delta (95% CI)	Original HRRs for local area treatment pattern IV 2SLS - XTIVREG code	Delta (95% CI)	Original HSAs for local area treatment pattern IV 2SLS - XTIVREG code	Delta (95% CI)
Mean Predicted 6-month cost										
BSC	36,703		36,533		36,562		36,523		35,421	
Chemotherapy	49,834	13,131 (11,671, 14,591)	49,533	13,000 (11,474, 14,526)	49,437	12,875 (11,354, 14,397)	52,562	16,039 (1,526, 30,552)	55,818	20,397 (9,299, 31,494)
Targeted	62,932	13,098 (11,367, 14,829)	60,528	10,995 (9,027, 12,964)	60,380	10,943 (8,919, 12,967)	58,702	6,140 (-7,688, 19,968)	57,019	1,202 (-10,815, 13,219)
Mean Predicted 12-month cost										
BSC	41,621		41,395		41,376		40,625		41,612	
Chemotherapy	65,456	23,835 (21,973, 25,812)	65,051	23,656 (21,443, 25, 869)	64,968	23,591 (21,355, 25,828)	69,411	28,785 (9,723, 47,847)	71,309	29,698 (15,147, 44,248)
Targeted	94,268	28,812 (26,395, 30,946)	89,818	24,767 (21,652, 27,883)	89,933	24,966 (21,781, 28,151)	90,243	20,832 (2,670, 38,995)	85,400	14,091 (-1,666, 29,847)

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**CHAPTER 2 ARE WE USING MOLECULARLY GUIDED THERAPY FOR LUNG
CANCER IN ROUTINE CARE? ANALYSIS OF MEDICARE PATIENTS WITH STAGE
IV NON-SMALL CELL LUNG CANCER (NSCLC)**

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2.1 Abstract

Purpose

Patients who test positive for epidermal growth factor receptor (*EGFR*) somatic alterations derive significant clinical benefits from erlotinib, but the extent to which individual lung cancer patients undergo molecular testing in routine care is not known. Prevalence and factors associated with testing in routine care were determined in elderly patients with stage IV NSCLC from SEER-Medicare.

Patients and Methods

We identified patients with squamous- and non-squamous-cell diagnosis of Stage IV NSCLC occurring between 2007 and 2009. The main outcome, molecular testing, was identified with relevant medical billing codes. Multivariable logistic regression was used to assess characteristics that independently determine the choice of molecular testing.

Results

Among 7,678 patients, only 4.9% underwent a molecular test. The strongest predictor of molecular testing was treating physician affiliation with a NCI cancer center (adjusted proportion: 9.9% at NCI cancer centers vs. 4.7% outside). Among the minority of patients who were tested, molecular testing was independently associated with phenotypic enrichment using known correlates of *EGFR* mutations (female gender, East Asian origin, non-squamous-cell histology, no history of COPD which was a proxy for being a non-smoker). Older age, enrollment in Medicaid, and admission to hospice decreased the likelihood of testing but increased the probability of first-line erlotinib

therapy. Among the 6.5% of patients who were treated with first-line erlotinib, only 8.9% of patients were tested prior to erlotinib initiation.

Conclusion

During the study period, the vast majority of lung cancer patients did not undergo molecular testing in routine care. Actions towards population-wide dissemination of molecular testing through provider education and payer mandates to submit molecular test results prior to reimbursement for targeted therapies may encourage adoption of these technologies.

2.2 Introduction

Treatment outcomes in advanced lung cancer have plateaued at a median overall survival (OS) of 10 to 12 months with traditional chemotherapy combinations, but targeted treatment innovations are changing the landscape of prognosis in lung cancer. The burden of lung cancer is substantial. It is the leading cause of cancer related mortality, representing 27% of all cancer deaths. In the United States alone, approximately 160,000 patients will die from this disease in 2014.¹ Evidence points to significant clinical benefits from therapies that target molecular pathways in patients who test positive for oncogenic driver mutations, but the extent to which individual lung cancer patients undergo molecular testing in routine care is not known.^{2,3}

Patients whose tumors are identified to carry epidermal growth factor receptor (*EGFR*) somatic alterations and who are treated with erlotinib have shown remarkable improvements in median progression free survival (PFS) compared to chemotherapy alone, 9.4 vs. 5.2 months.² On the other hand, controlled trial-based evidence suggests that conventional chemotherapy confers better outcomes in patients with *EGFR* wild type tumors compared to *EGFR* TKI therapy.³⁻⁶ *EGFR* gene mutations are more prevalent in non-squamous tumors, women, patients of East Asian origin and in those with no history of smoking.⁴ While phenotypic characteristics associated with these gene mutations have been elucidated, these attributes do not adequately discriminate between *EGFR* mutation positive and wild type tumors. There is a general consensus that phenotypic characteristics should not be used to select or exclude patients for treatment or molecular testing.⁴ By 2007, the National Comprehensive Cancer Network (NCCN) Lung Cancer guidelines acknowledged the predictive value of

EGFR gene mutations for response to erlotinib.¹⁰ Beginning in 2010, guideline recommendations endorsed population-wide molecular screening for *EGFR* gene mutations in all advanced non-squamous, stage IV NSCLC cases to inform treatment choices.^{4,7,8}

In this analysis, our goal was to estimate the prevalence of molecular screening in routine care and to assess factors that determine the choice to conduct molecular testing in a nationally representative cohort of elderly patients with stage IV NSCLC.

2.3 Methods

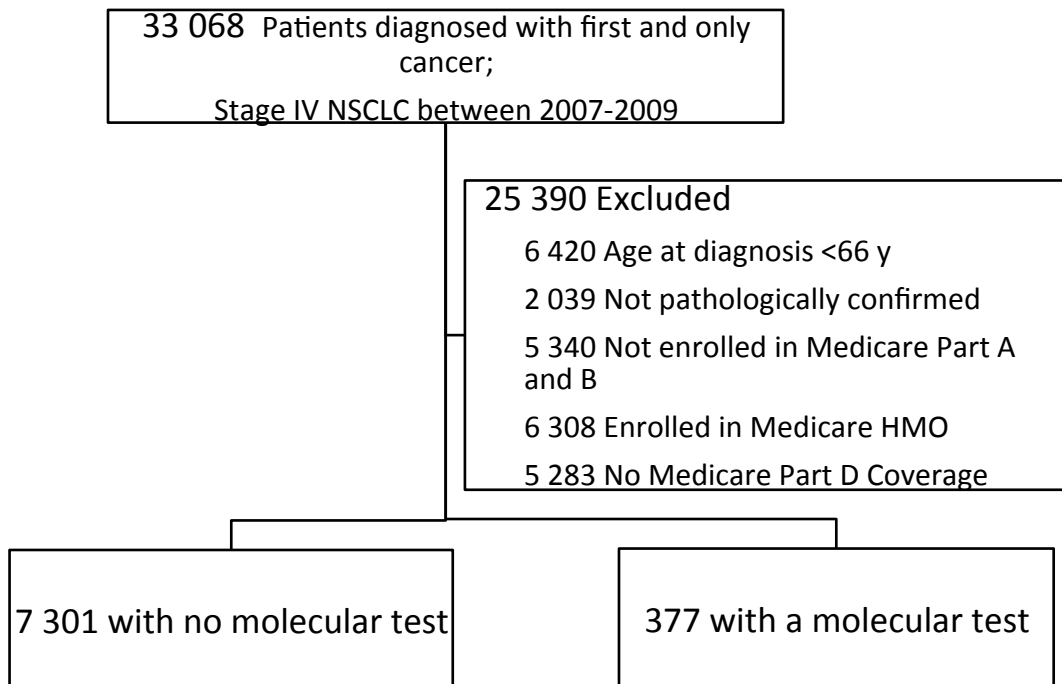
2.3.1 Study Participants

We identified patients with pathologically confirmed squamous cell and non-squamous cell incident diagnosis of Stage IV NSCLC occurring between January 1, 2007 and December 31, 2009. We used data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program linked to Medicare Part A, B and D claims. The SEER program collects information from 17 cancer registries, which cover approximately 28% of the US population.⁹

To ascertain comorbidity burden and pre-diagnosis medical costs at baseline and to determine lung cancer treatment practice patterns after diagnosis, patients who were continuously enrolled in Medicare Part A and B beginning eight months prior to diagnosis and those who were also eligible for Parts A, B and D one year post diagnosis were included. To ensure completeness of claim history, patients who were in a health maintenance organization (HMO) plan at any point during the observation period were excluded. In addition, patients were excluded if they had other concurrent cancers

diagnosed either before or after the index NSCLC diagnosis. In the primary analysis, we compared patient groups according to whether or not they underwent a molecular test after diagnosis and prior to treatment initiation (Figure 2.1). In a secondary analysis in which we examined determinants of first-line therapy, we classified patients into three groups based on first-line treatment initiation within 120 days of diagnosis: 1) erlotinib group; 2) chemotherapy group, which comprised of patients who were treated with chemotherapy, with or without bevacizumab; 3) remaining patients were categorized to the best supportive care (BSC) group, if there was no evidence of systemic therapy receipt (chemotherapy or targeted therapy) within 120 days from diagnosis.

Figure 2.1. Flow diagram of study cohort



2.3.2 Molecular Test Identification

During the observation period between 2007 and 2010, a unique Healthcare Common Procedure Coding System (HCPCS) code to allow identification of *EGFR* mutation testing did not exist. Instead, providers deferred to a ‘stacking’ method to bill for *EGFR* gene mutation analysis using HCPCS codes that represented the steps and techniques used in performing a molecular pathology test. We used the Genzyme Genetics (the sole distributor of the commercial *EGFR* assay in 2010) test stack of HCPCS codes to identify any claim in the outpatient file with at least one of these codes (see Appendix). Even in 2010, the vast majority of laboratories (99%) were not accredited by the Clinical Laboratory Improvement Amendments (CLIA) program to conduct cytogenetic testing and ordered molecular testing through commercial reference laboratories.¹⁰ Those that were accredited and conducted *EGFR* mutation analysis with laboratory developed tests (LDTs) also used the ‘stacking’ method for billing purposes with a combination of the HCPCS codes outlined in the Appendix.(personal communication: J. Fahey, December 2013). We also flagged HCPCS code 83912 (‘Interpretation and report’) in the physician claims file, as an indicator of a molecular test. This code corresponds to the professional component of the molecular test bill and appears in the physician file irrespective of whether the test was conducted as part of an inpatient or an outpatient encounter. (personal communication: J.Fahey, December 2013) Therefore, while a *specific* molecular test, such as *KRAS* or *EGFR* gene mutation analysis, could not be identified in the claims during the index period, performance of *any* molecular test was identifiable. The index period for molecular test classification encompassed claims with dates ranging from 45 days prior to diagnosis through 30 days after the start of first line therapy, or 150 days

after diagnosis for patients who were managed with BSC. Both the index period and the composition of our analytic cohort, which comprised newly diagnosed stage IV NSCLC patients with lung cancer being the first and only cancer, mitigated misclassification bias of a molecular test order for other conditions.

2.3.3 First-line Treatment Classification

We identified cancer directed systemic therapy use from Medicare claims. Claims for individual drugs were flagged using HCPCS codes and National Drug Codes (NDC) in the outpatient, physician, durable medical equipment and Medicare Part D files using previously described methods.^{11,12} The date of the first systemic therapy claim within 120 days from diagnosis was used to define the start date of first line treatment.¹³

2.3.4 Patient and Practice Characteristics

We identified several potential factors that may impact decisions surrounding molecular testing and first line treatment choice. These spanned phenotypic characteristics that are correlated with presence of drug sensitizing *EGFR* gene mutations in NSCLC - race, female gender, histology, and smoking history using presence of COPD as a proxy indicator. Additional characteristics included: age; ethnicity; comorbidity score; hospice enrollment after diagnosis; marital status; presence of brain metastases; enrollment in Medicaid; sample acquisition method (histology, cytology); urban residence; US Census tract level household income, college education; year of diagnosis and SEER Region.¹⁴ A proxy measure of poor performance status (PS) prior to diagnosis was also included based on bills starting from 8 months prior to diagnosis. Services typically associated with poor functional status were coded as

dummies (inpatient or skilled nursing facility stay, home health visit, use of home oxygen, or ADL aids (any bill for equipment such as walkers, hospital beds, wheelchairs), personal communication: E. Lamont, November, 2013).¹⁵ These indicators were summed up as a count (0, 1, 2+) to derive the proxy PS index. Furthermore, we summed up medical spending for the eight-month period prior to diagnosis as another proxy indicator of health status (excluding 2 months most proximal to diagnosis to exclude costs related to cancer diagnosis and staging). Practice characteristics, namely National Cancer Institute (NCI) cancer center designation, cooperative group affiliation, and hospital teaching status, were also included.

2.3.5 Statistical Methods

Bivariate analyses using the χ^2 test were conducted to compare the distributions in baseline characteristics according to molecular test status. Next, we used logistic regression to identify patient and practice characteristics associated with a molecular test order. Included in the model were variables with a p-value <0.20 on bivariate testing. Marginal, adjusted probabilities were calculated for each variable in the multivariable model. A parallel method was used to construct a multivariable model using multinomial logistic regression to identify patient, disease and practice characteristics associated with first line treatment (erlotinib, chemotherapy, BSC; see Appendix). We also conducted survival analyses to explore the relationship between time to hospice admission from initiation of first-line therapy and molecular testing. Kaplan-Meier survival curves were generated and subgroups were compared using the log rank test. All analyses were conducted using SAS, version 9.2.

2.4 Results

2.4.1 Baseline Characteristics

Among 7,678 incident cases diagnosed with Stage IV non-squamous and squamous cell NSCLC between 2007 and 2009, who met our inclusion criteria (Figure 2.1), only 377 (4.9%) underwent a molecular test. Table 2.1 summarizes patient and practice characteristics according to whether or not a molecular test was performed. Among patients who were tested compared to those who were not, a higher proportion were females (58.4% vs. 51.2%), of East Asian origin (11.4% vs. 7.2%), with no history of COPD (a proxy indicator of smoking, 84.9% vs. 71.5%) and had non-squamous cell tumors (88.6% vs. 76.3%). In addition, younger patients, those with no proxy indicators of poor PS, and no comorbidities had a higher likelihood of being tested. Hospice admission after diagnosis and enrollment in Medicaid were both associated with a lower probability of a molecular test. Persons treated at NCI designated cancer centers and at practices with a cooperative group affiliation were also more likely to undergo molecular testing (10.1% vs. 2.0%, and 30.8% vs. 16.1%, respectively). A higher proportion of patients who received any systemic cancer-directed therapy (7.8%) underwent a molecular test compared to those managed with BSC (1.7%), but unadjusted prevalence of testing was low across all treatment categories.

Table 2.1. Characteristics according to molecular testing status.

	Characteristic*	Molecular Test (n=377)	No Molecular Test (n=7,301)
Age at diagnosis, years	66-69	107 (28.4)	1,636 (22.4)
	70-74	104 (27.6)	1,950 (26.7)
	75-79	90 (23.9)	1,697 (23.2)
	80-84	59 (15.7)	1,257 (17.2)
	85+	17 (4.5)	761 (10.4)
Gender	Female	220 (58.4)	3,737 (51.2)
Race	White	314 (83.3)	5,951 (81.5)
	Black	14 (3.7)	753 (10.3)
	East Asian	43 (11.4)	525 (7.2)
	Other	6 (1.6)	72 (1.0)
Ethnicity	Hispanic	19 (5.0)	414 (5.7)
Baseline PS indicator, count	0	220 (58.4)	3,141 (43.0)
	1	100 (26.5)	2,186 (29.9)
	2+	57 (15.1)	1,974 (27.0)
Marital Status	Married	206 (54.6)	3,256 (44.6)
Comorbidity Index	0	262 (69.5)	4,210 (57.7)
	1	59 (15.7)	1,314 (18.0)
	2	28 (7.4)	682 (9.3)
	3+	28 (7.4)	1,095 (15.0)
COPD	Yes	57 (15.1)	2,079 (28.5)
	No	320 (84.9)	5,222 (71.5)
Histology	Non-squamous cell	334 (88.6)	5,573 (76.3)
	Squamous cell	43 (11.4)	1,728 (23.7)
Sample acquisition method	Histology	309 (82.0)	5,440 (74.5)
	Cytology	68 (18.0)	1,861 (25.5)
Brain Metastases	Present	69 (18.3)	1,296 (17.8)
Hospice admission	Yes	149 (39.5)	4,370 (59.9)
Prior Year Medicaid	Yes	72 (19.1)	2,617 (35.8)
First-line Treatment	Erlotinib	43 (11.4)	457 (6.3)
	Chemotherapy with/without bevacizumab	270 (61.7)	3,244 (44.4)
	Best supportive care	64 (17.0)	3,600 (49.3)
Urban Residence	Yes	355 (94.2)	6,299 (86.3)
Cooperative Group affiliation	Yes	116 (30.8)	1,175 (16.1)
NCI Cancer Center	Yes	38 (10.1)	146 (2.0)
Teaching Hospital	Yes	102 (27.1)	1,053 (14.4)
College education (census tract quintile)	1 (low)	34 (9.0)	1,733 (23.7)
	2	58 (15.4)	1,551 (21.2)
	3	80 (21.2)	1,354 (18.6)
	4	77 (20.4)	1,350 (18.5)
	5 (high)	128 (34.0)	1,309 (17.9)
Income (census tract quintile)	1 (low)	40 (10.6)	1,784 (24.4)
	2	54 (14.3)	1,573 (21.5)
	3	79 (21.0)	1,381 (18.9)
	4	78 (20.7)	1,320 (18.1)
	5 (high)	126 (33.4)	1,239 (17.0)
1-yr Cost pre diagnosis (quintile)	1 (low)	63 (16.7)	1,176 (16.1)
	2	87 (23.1)	1,436 (19.7)
	3	92 (24.4)	1,460 (20.0)
	4	70 (18.6)	1,583 (21.7)
	5 (high)	65 (17.2)	1,646 (22.5)
Year of diagnosis	2007	40 (10.6)	2,538 (34.8)
	2008	88 (23.3)	2,447 (33.5)
	2009	249 (66.1)	2,316 (31.7)
Region	Northeast	122 (32.4)	1,321 (18.1)
	South	52 (13.8)	2,123 (29.1)
	Midwest	35 (9.3)	1,155 (15.8)
	West	168 (44.6)	2,702 (37.0)

2.4.2 Predictors of Molecular Testing

Table 2.2 summarizes the significant characteristics, which determined the decision to perform a molecular test. First, the strongest independent predictor of molecular testing was affiliation with a NCI cancer center (adjusted proportion: 9.9% at NCI cancer centers vs. 4.7% outside). Second, the multivariable prediction model suggested that molecular testing was also associated with phenotypic enrichment using known correlates of *EGFR* mutations. The adjusted predicted probabilities of undergoing a molecular test by phenotype were: 5.5% for females vs. 4.3% for males; 3.3% for non-squamous cell vs. 2.3% for squamous cell histology; 8.0% for East Asian vs. 3.1% for Black racial origin for example; and 5.3% for no COPD (a proxy indicator of smoking status) vs. 3.4% for COPD, respectively (p-values <0.01). Notably among all gender-race groups, East Asian, female patients had the highest probability of being tested and also of initiating first-line erlotinib therapy (Figure 2.2). But, even among this patient subgroup, the adjusted proportions with testing and TKI treatment were only 8.9% and 14.2%, respectively. As expected, histological tissue samples were associated with a higher probability of molecular testing than cytological samples (adjusted proportions: 5.4% vs. 3.4%).

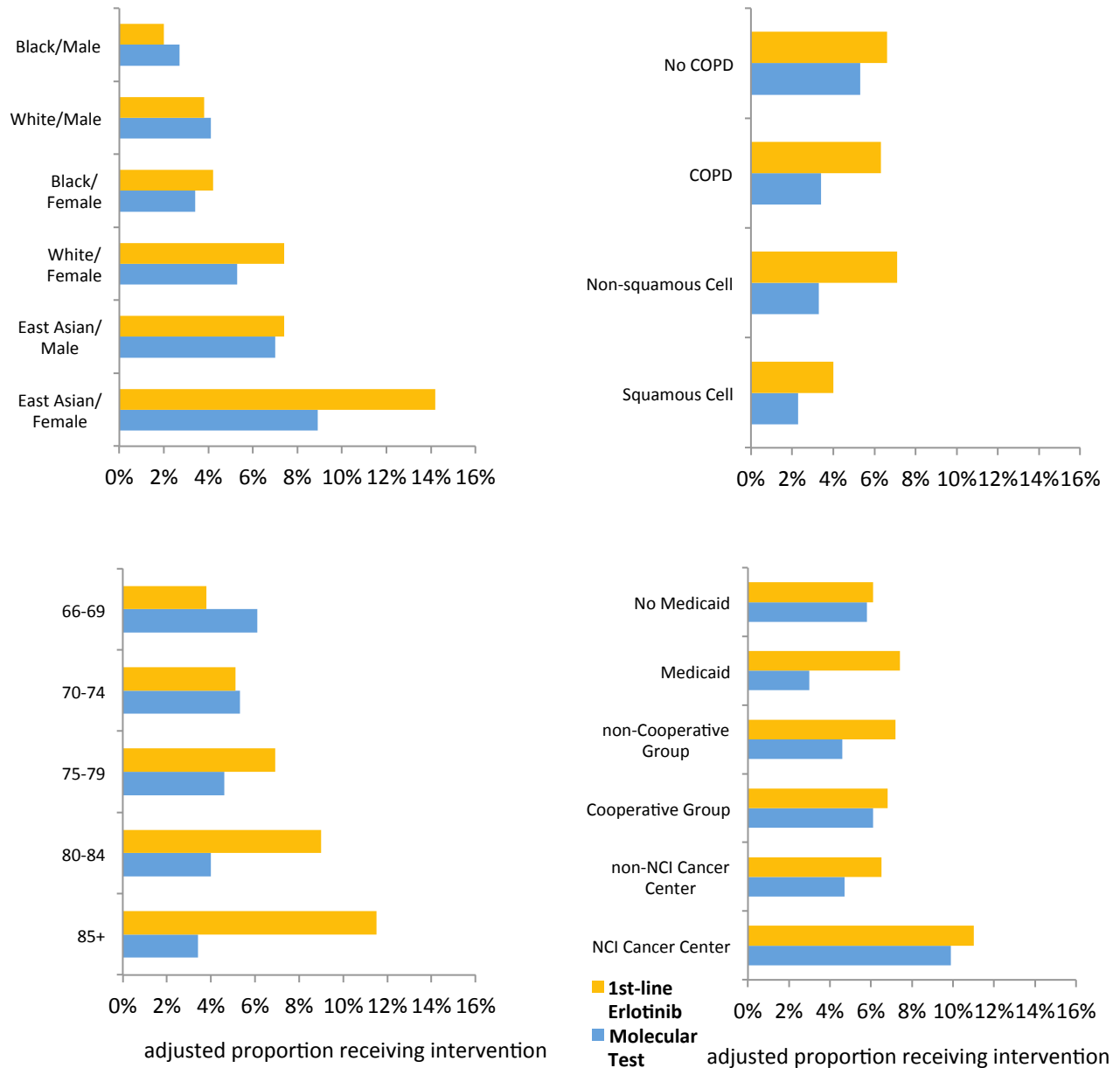
Table 2.2. Predictors of molecular testing

Characteristic	Odds Ratio (OR)	95% CI for OR	P-value	Adjusted Probability of a Molecular Test (%)
Gender				
Male	Reference	Reference		4.3
Female	1.35	1.08, 1.69	<0.01	5.5
Age at diagnosis, years				
66-69	Reference	Reference		6.1
70-74	0.82	0.61, 1.11	0.20	5.3
75-79	0.80	0.59, 1.09	0.16	4.6
80-84	0.68	0.48, 0.96	0.03	4.0
85+	0.35	0.20, 0.60	<0.01	3.4
Race				
White	Reference	Reference		4.8
Black	0.61	0.35, 1.08	0.10	3.1
East Asian	1.91	1.28, 2.85	<0.01	8.0
Other	1.33	0.53, 3.37	0.55	6.5
Baseline PS indicator				
0	Reference	Reference		5.4
1	0.82	0.63, 1.06	0.13	4.8
2+	0.70	0.50, 0.96	0.03	3.7
Histology				
Non-squamous cell	Reference	Reference		3.3
Squamous cell	0.47	0.34, 0.66	<0.01	2.3
COPD				
Yes	Reference	Reference		3.4
No	1.71	1.26, 2.33	<0.01	5.3
Sample acquisition method				
Histology	Reference	Reference		5.4
Cytology	0.58	0.43, 0.77	<0.01	3.4
Prior year, Medicaid				
Yes	Reference	Reference		3.0
No	2.07	1.52, 2.82	<0.01	5.8
Income (census tract quintile)				
1 (Low)	Reference	Reference		3.4
2	1.28	0.83, 1.97	0.26	4.0
3	1.71	1.13, 2.58	0.01	4.7
4	1.53	1.00, 2.34	<0.05	5.5
5 (High)	2.31	1.53, 3.47	<0.01	6.3
NCI Cancer Center				
No	Reference	Reference		4.7
Yes	2.59	1.62, 4.12	<0.01	9.9
Cooperative Group Affiliation				
No	Reference	Reference		4.6
Yes	1.39	1.05, 1.84	0.02	6.1
Hospice				
No	Reference	Reference		6.5
Yes	0.49	0.39, 0.62	<0.01	3.6
Region				
Northeast	Reference	Reference		7.0
South	0.41	0.28, 0.59	<0.01	3.3
Midwest	0.39	0.26, 0.59	<0.01	3.1
West	0.69	0.52, 0.91	0.01	5.3
Year of diagnosis				
2007	Reference	Reference		1.6
2008	2.44	1.66, 3.59	<0.01	3.7
2009	7.03	4.97, 9.95	<0.01	9.0

Patient characteristics that are not correlated with *EGFR* mutation status, namely younger age and better baseline PS, also affected the likelihood of molecular testing. For example, the youngest patients in our cohort (aged 66 to 69 years) were more likely to have a molecular test (6.1%) compared to the age group 80 to 84 years (4.0%). Interestingly, an opposite relationship emerged between age and the likelihood of receipt of first-line erlotinib (Figure 2.2). Older age was associated with a higher probability of treatment with the oral TKI (adjusted proportion: 3.8% for age group 66 to 69 years vs. 9.0% for age group 80 to 84 years). Persons with no indicators of a poor PS had a 5.4% adjusted probability of testing compared to 3.7% in those with 2 or more indicators of poor PS. Controlling for age, indicators of a poor PS, and other significant characteristics, admission to a hospice after diagnosis of NSCLC was a strong determinant of both molecular testing and initiation of first-line erlotinib therapy. Patients who enrolled in hospice care had a significantly lower likelihood of undergoing molecular testing (adjusted proportion: 3.6% with vs. 6.5% without hospice admission, p-value <0.01), but a significantly higher likelihood of initiating first-line erlotinib therapy (7.2% with vs. 5.6% without hospice admission, p-value <0.01).

NCI Cancer Center designation notwithstanding, other practice characteristics that independently determined testing included Medicaid enrollment and cooperative group affiliation. Notably, Medicaid enrollment was a negative independent predictor of molecular testing (adjusted proportion: 3.0% with Medicaid vs. 5.8% without), but it was a positive predictor of first-line erlotinib therapy (adjusted proportion: 7.4% with Medicaid vs. 6.1% without, Figure 2.2).

Figure 2.2. Adjusted relationships between patient and practice characteristics and receipt of first-line erlotinib therapy (yellow bars) and undergoing a molecular test (blue bars) for Stage IV NSCLC. Proportions are the average predicted probabilities adjusted for other covariates in regression models (Table 2.2 and Appendix).

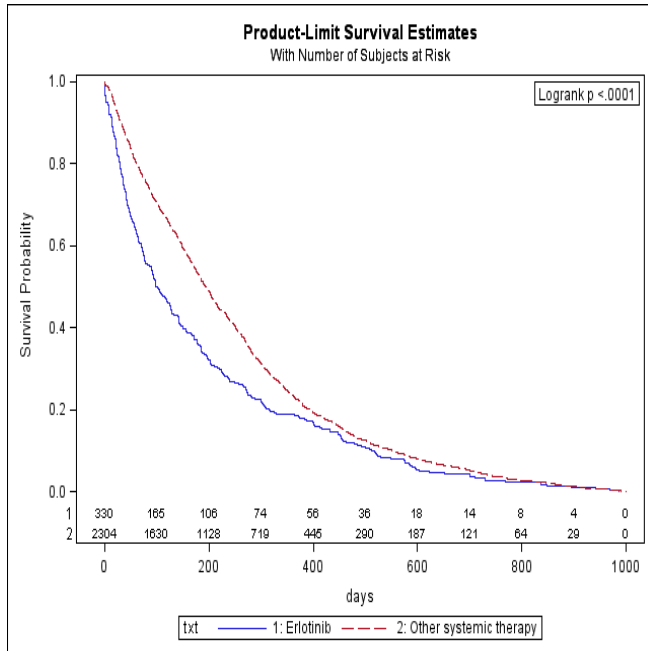


Likewise, more patients treated at practices with a cooperative group affiliation underwent molecular testing (adjusted proportion: 6.1% vs. 4.6%), but fewer were treated with first-line erlotinib (adjusted proportion: 6.8% vs. 7.2%) compared to patients from other centers. Furthermore, some regions appeared to be earlier adopters of molecular testing in lung cancer, albeit the rates of utilization were low across all regions. For instance, in the Northeast, which ranked highest in molecular test adoption rates, the adjusted proportion was only 7.0%. Although we did observe a significant time trend for molecular testing after controlling for other predictors, still only 9.0% of patients were tested in 2009, from a low of 1.6% in 2007.

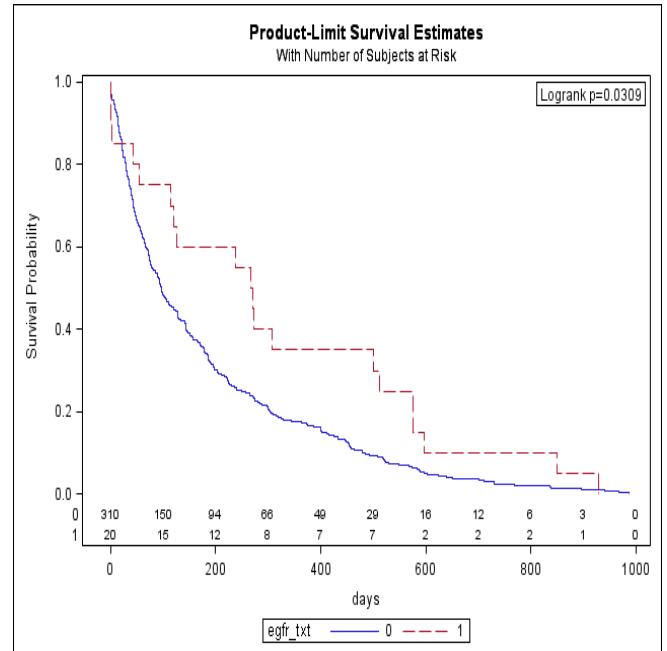
Given that hospice admission emerged as a significant indicator of both molecular testing and of first-line erlotinib therapy initiation, we explored the association between the start of treatment and time to admission to a hospice and according to whether or not molecular testing was performed (Figure 2.3). Among patients who received hospice care, the median time to hospice admission was 3.3 months after start of first-line erlotinib and 6.6 months after initiation of chemotherapy-based treatment (p -value <0.0001). The median time to hospice admission from start of first-line erlotinib was 3.2 months among persons who did not undergo molecular testing ($n=310$) and 8.9 months among those who were tested ($n=20$), p -value=0.03. Twenty-five percent of patients who did not have molecular testing were admitted to a hospice approximately within one month (35 days) after starting first-line erlotinib compared to 2.8 months if they were tested (Figure 2.3).

Figure 2.3. Kaplan-Meier curves depicting time to hospice admission from initiation of first line therapy among Stage IV NSCLC patients admitted to a hospice.

A



B



(A) Time from first-line erlotinib initiation (blue curve, n=330) and from first-line chemotherapy initiation (red curve, n=2304) to hospice admission. (B) Time from first-line erlotinib initiation among patients with a molecular test (red curve, n=20) and those without a molecular test (blue curve, n=310) to hospice admission.

2.5 Discussion

Molecularly guided therapy has revolutionized the prognosis of lung cancer. Using the SEER-Medicare linked data, we evaluated practice patterns of molecular testing in routine care among patients with stage IV NSCLC diagnosed between 2007 and 2009. In our population-based study, only 4.9% of eligible patients underwent molecular testing. The determination to conduct molecular testing was influenced by phenotypic characteristics that are correlated with *EGFR* mutations, younger age, and better performance status. Patients enrolled in Medicaid and those admitted to hospice after diagnosis were significantly less likely to undergo molecular testing, but had a higher likelihood of initiating first-line erlotinib therapy. The strongest predictor of having a molecular test was receipt of care at an NCI designated cancer center.

Corroborating evidence of the underuse of predictive biomarker screening in lung cancer comes from a hospital-level analysis by Lynch et al.¹⁰ In that paper, the authors estimated that in 2010, only 12% of US acute care hospitals ordered an *EGFR* assay, which represented 5.7% of newly diagnosed lung cancer patients. From our analysis of individual patients, the adjusted proportion of patients diagnosed in 2009 who had any type of molecular test was 9.0%. This estimate may include non-*EGFR* molecular tests, such as *KRAS* gene mutation testing. Still, it appears that molecular testing is performed in a minority of patients who are treated in routine care. Even at centers of excellence, the NCI cancer centers, the adjusted proportion of patients who were tested was only 9.9%. These findings call for a closer examination of the barriers to dissemination of molecular testing. For example, new evidence suggests that

physicians may have a low confidence in genomic knowledge.¹⁶ These knowledge gaps may signal important patient-access barriers at the provider level.

Our results further indicate that in routine care clinical enrichment criteria were used to select patients for molecular testing. All clinical characteristics associated with EGFR mutations (female gender, smoking history, East Asian race) were independent predictors of molecular testing. Such clinical enrichment practices do not have adequate discriminatory power as a pre-screening tool.⁴ One study reported that basing molecular screening on clinical enrichment criteria may lead to undiagnosing over half of patients who carry drug sensitizing mutations.¹⁷ With the advent of multiplexed test platforms, population-wide screening for predictive biomarkers in lung cancer followed by molecularly guided therapy is a cost effective approach (D.Romanus, Cost-Effectiveness of Multiplexed Predictive Biomarker Screening in Non-Small Cell Lung Cancer. Manuscript submitted for publication). At the payer level, payment for targeted therapies with identifiable predictive molecular markers could be made contingent on evidence of test results to encourage molecularly guided therapy.

First-line therapy with erlotinib in patients harboring EGFR sensitizing mutations is the accepted standard of care.^{7,18} Utilization of first-line TKI therapy in unselected patients is controversial.³ In our analysis, only 8.6% of patients had a molecular test prior to initiation of first-line erlotinib. Among patients on first-line erlotinib, 66% were admitted to a hospice. In unselected patients, the median time to hospice admission was 3 months and a quarter of patients were admitted within approximately one month from initiation of first-line erlotinib. First-line treatment with erlotinib in unselected

patients and its value in the setting of an imminent hospice admission warrant closer examination in future research.

Several limitations need to be taken into account when interpreting our results. We were unable to categorize tests by specific molecular markers due to the lack of billing codes that would identify each genetic mutation tested. We flagged any code that was part of the stack of codes used for billing for an *EGFR* gene mutation test during the period we analyzed to indicate that a molecular test was conducted. Even if our estimates represent the upper bound of *EGFR* mutation testing to inform first line therapy, our results suggest a gross underutilization of molecularly guided therapy. This analysis was based on a cohort of elderly patients with fee-for-service (FFS) and Medicare Part D benefits. While two-thirds of lung cancer patients are older than 65 at time of diagnosis, beneficiaries of FFS and Medicare D coverage may differ systematically from those in Medicare Advantage.^{19,20}

Using the most recent SEER-Medicare data, we found that molecularly guided therapy was underutilized in routine care of patients diagnosed with advanced NSCLC between 2007 and 2009. The minority of patients who did undergo molecular testing (4.9%) appeared to be selected for testing based on clinical enrichment criteria and nonmedical factors, such as practice setting and socioeconomic status. Actions towards population-wide dissemination of molecular testing through provider education and payer mandates to submit molecular test results prior to reimbursement for targeted therapies may encourage adoption of these technologies. Future studies should be conducted to evaluate the impact of recent guideline recommendations for population-

wide *EGFR* mutation screening on the dissemination of genomic testing and molecularly guided therapy.^{4,7}

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2.7 Appendix

Table 2.A.1. Codes Used in Defining Molecular Tests.

CARRIER CLAIMS	
83912	MOLECULAR DIAGNOSTICS; INTERPRETATION AND REPORT
OUTPATIENT CLAIMS	
83890	MOLECULAR DIAGNOSTICS; MOLECULAR ISOLATION OR EXTRACTION, EACH NUCLEIC ACID TYPE (IE, DNA OR RNA)
83891	MOLECULAR DIAGNOSTICS; ISOLATION OR EXTRACTION OF HIGHLY PURIFIED NUCLEIC ACID, EACH NUCLEIC ACID TYPE (IE, DNA OR RNA)
83892	MOLECULAR DIAGNOSTICS; ENZYMATIC DIGESTION, EACH ENZYME TREATMENT
83894	MOLECULAR DIAGNOSTICS; SEPARATION BY GEL ELECTROPHORESIS (EG, AGAROSE, POLYACRYLAMIDE), EACH NUCLEIC ACID PREPARATION
83896	MOLECULAR DIAGNOSTICS; NUCLEIC ACID PROBE, EACH
83898	MOLECULAR DIAGNOSTICS; AMPLIFICATION, TARGET, EACH NUCLEIC ACID SEQUENCE
83900	MOLECULAR DIAGNOSTICS; AMPLIFICATION, TARGET, MULTIPLEX, FIRST 2 NUCLEIC ACID SEQUENCES
83901	MOLECULAR DIAGNOSTICS; AMPLIFICATION, TARGET, MULTIPLEX, EACH ADDITIONAL NUCLEIC ACID SEQUENCE BEYOND 2 (LIST SEPARATELY IN ADDITION TO CODE FOR PRIMARY PROCEDURE)
83902	MOLECULAR DIAGNOSTICS; REVERSE TRANSCRIPTION
83903	MOLECULAR DIAGNOSTICS; MUTATION SCANNING, BY PHYSICAL PROPERTIES (EG, SINGLE STRAND CONFORMATIONAL POLYMORPHISMS [SSCP], HETERODUPLEX, DENATURING GRADIENT GEL ELECTROPHORESIS [DGGE], RNA'ASE A), SINGLE SEGMENT, EACH
83904	MOLECULAR DIAGNOSTICS; MUTATION IDENTIFICATION BY SEQUENCING, SINGLE SEGMENT, EACH SEGMENT
83907	MOLECULAR DIAGNOSTICS; LYSIS OF CELLS PRIOR TO NUCLEIC ACID EXTRACTION (EG, STOOL SPECIMENS, PARAFFIN EMBEDDED TISSUE), EACH SPECIMEN
83909	MOLECULAR DIAGNOSTICS; SEPARATION AND IDENTIFICATION BY HIGH RESOLUTION TECHNIQUE (EG, CAPILLARY ELECTROPHORESIS), EACH NUCLEIC ACID PREPARATION
83914	MUTATION IDENTIFICATION BY ENZYMATIC LIGATION OR PRIMER EXTENSION, SINGLE SEGMENT, EACH SEGMENT (EG, OLIGONUCLEOTIDE LIGATION ASSAY [OLA], SINGLE BASE CHAIN EXTENSION [SBCE], OR ALLELE-SPECIFIC PRIMER EXTENSION [ASPE])
83912	MOLECULAR DIAGNOSTICS; INTERPRETATION AND REPORT

Table 2.A.2. Predictors of first line erlotinib therapy.

Variable		OR**	95% CI for OR
Gender	Male	Reference	Reference
	Female	2.16	1.72, 2.70
Age at diagnosis, years	66-69	Reference	Reference
	70-74	1.36	0.96, 1.92
	75-79	2.28	1.63, 3.19
	80-84	4.35	3.09, 6.14
	85+	9.08	6.01, 13.73
Race	White	Reference	Reference
	Black	0.98	0.63, 1.52
	East Asian	4.50	3.26, 6.22
	Other	2.44	1.01, 5.88
Comorbidity Index	0	Reference	Reference
	1	1.20	0.91, 1.59
	2	1.18	0.82, 1.71
	3+	1.27	0.90, 1.80
Baseline PS indicator	0	Reference	Reference
	1	1.01	0.79, 1.29
	2+	1.25	0.95, 1.64
Histology	Non-squamous cell	Reference	Reference
	Squamous cell	0.56	0.42, 0.75
Brain metastases	No	Reference	Reference
	Yes	1.37	1.04, 1.81
COPD	No	Reference	Reference
	Yes	1.16	0.89, 1.50
Molecular test prior to treatment	No	Reference	Reference
	Yes	1.22	0.84, 1.77
Prior year, Medicaid	Yes	Reference	Reference
	No	0.60	0.47, 0.76
Marital status	Not married	Reference	Reference
	Married	0.97	0.77, 1.21
Income (census tract quintile)	1 (Low)	Reference	Reference
	2	1.15	0.83, 1.60
	3	1.21	0.86, 1.69
	4	1.23	0.88, 1.73
	5 (High)	1.32	0.93, 1.86
NCI Cancer Center	No	Reference	Reference
	Yes	1.15	0.53, 2.47
Cooperative Group Affiliation	No	Reference	Reference
	Yes	0.25	0.18, 0.34
Hospice	No	Reference	Reference
	Yes	1.79	1.42, 2.26
Region	Northeast	Reference	Reference
	South	0.85	0.60, 1.18
	Midwest	0.67	0.45, 0.99
	West	0.90	0.67, 1.22

*multivariable, multinomial logistic model controlled for all variables in the table

** compared to first line chemotherapy

CHAPTER 3 COST-EFFECTIVENESS OF MULTIPLEXED PREDICTIVE BIOMARKER SCREENING IN NON-SMALL CELL LUNG CANCER

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3.1 Abstract

Purpose

Population-wide screening for epidermal growth factor receptor (*EGFR*) mutations and anaplastic lymphoma kinase (*ALK*) gene rearrangements to inform cancer therapy in non-small cell lung cancer (NSCLC) is recommended by guidelines. We estimated cost-effectiveness of multiplexed predictive biomarker screening in metastatic NSCLC from a societal perspective in the US.

Patients and Methods

We constructed a microsimulation model to compare the life expectancy and costs of multiplexed testing and molecularly guided therapy vs treatment with cisplatin-pemetrexed (CisPem). All testing interventions included a two-step algorithm of concurrent *EGFR* mutation and *ALK* overexpression testing with immunohistochemistry (IHC) followed by *ALK* rearrangement confirmation with a fluorescence in situ hybridization (FISH) assay for IHC positive results. Three strategies were included: 'Test-treat' approach, where molecularly guided therapy was initiated after obtainment of test results; 'Empiric switch therapy', with concurrent initiation of CisPem and testing and immediate switch to test-result conditional treatment after one cycle of CisPem; and 'Empiric therapy' approach in which CisPem was continued for four cycles before start of a tyrosine kinase inhibitor (TKI).

Results

The incremental cost-effectiveness ratio (ICER) for 'Test-treat' compared to treatment with CisPem was \$150,000 per quality-adjusted life year (QALY) gained. Both empiric

treatment approaches had less favorable ICERs. 'Test-treat' and 'Empiric switch therapy' yielded higher expected outcomes in terms of QALYs and life-years (LYs) than 'Empiric therapy'. These results were robust across plausible ranges of model inputs.

Conclusion

From a societal perspective, our cost-effectiveness results support the value of multiplexed genetic screening and molecularly guided therapy in metastatic NSCLC.

3.2 Introduction

The expansion of targeted therapeutic options for metastatic NSCLC is a welcome advance in a disease that historically has been resistant to treatment. Of the estimated 230,000 incident lung cancer cases annually, approximately 85% are diagnosed with NSCLC.[1, 2] Most patients present with advanced disease, and adenocarcinoma is the most common histologic subtype. [2] Somatic mutations in *EGFR* and *ALK* gene rearrangements are found in 9.5% and 3.9% of unselected NSCLCs, respectively.[3] Patients whose tumors carry a sensitizing mutation of *EGFR* or *ALK* gene rearrangements experience higher response rates, longer progression-free survival (PFS), and improved quality of life when treated with a TKI compared to platinum-based doublet chemotherapy.[6-7] Guidelines recommend the ascertainment of *EGFR* and *ALK* mutational status to help guide first-line systemic therapy in all patients with non-squamous, advanced NSCLC.[8] According to these recommendations, over 130,000 newly diagnosed NSCLC patients each year should undergo predictive biomarker screening.[9] But, biomarker screening appears to be underutilized in routine care. Only 12% of acute-care hospitals in the US used the *EGFR* assay in 2010, which represented only 5.7% of guideline-directed patients. [8, 9]

Even among patients whose tumors are tested for predictive biomarkers, uncertainty surrounding the optimal timing of TKI therapy initiation adds to the complexity of treatment decision-making.[10] The time required to perform molecular tests with sufficient tissue for analysis may tip the scale towards commencing empiric treatment with chemotherapy. Once test results reveal the presence of an actionable mutation after empiric therapy is begun, indirect evidence suggests that continuation of

chemotherapy for four to six cycles before switching to a TKI may optimize outcomes.[10, 11] In the present analysis, we compared a number of TKI initiation strategies.

Additionally, turn-around-time (TAT), the time from tissue sample acquisition to reporting of test results, and tissue sample adequacy are important considerations in patients with metastatic NSCLC. Multiplex detection of mutations has the advantage of tissue preservation and faster TAT. To date, economic analyses of screening for drug sensitivity biomarkers in lung cancer have restricted their focus on single biomarkers.[12-21] We examined two molecular markers, *EGFR* mutations and *ALK* rearrangements, for which the evidence is sufficiently mature to support population-wide screening.[8] The goal of this paper was to assess the cost-effectiveness of multiplexed predictive biomarker screening from a societal perspective in patients newly diagnosed with metastatic NSCLC living in the US.

3.3 Methods

3.3.1. Model and Treatment Strategies

We constructed a microsimulation, state-transition model to estimate the life expectancy and costs of four strategies: a 'No Test' approach, treatment with cisplatin-pemetrexed chemotherapy and no biomarker testing; two different empiric treatment strategies in which cisplatin-pemetrexed was initiated with concurrent biomarker testing. In one, the 'Empiric therapy' strategy, chemotherapy was continued for four cycles followed by TKI maintenance treatment in mutation-positive patients. In the other, the 'Empiric switch therapy', patients initiated first-line chemotherapy and those with

mutation positive tumors switched to a TKI immediately upon return of test results; and finally, the 'Test-treat' strategy, in which treatment was initiated only after results of testing became available. The simulated study population comprised of newly diagnosed stage IV NSCLC patients with non-squamous histology.

Figure 3.1 depicts the structure of the model. For all testing strategies, patients entered the model in the prescreen state on the day the test was ordered. If the sample was suitable for testing, the patient transitioned to the test sequence health states. With a daily cycle length, we were able to model wait times for test results prior to initiation of therapy. Patients with insufficient tumor samples from initial diagnostic samples transitioned to the rebiopsy prescreen state to account for elapsed time in determining appropriateness for a rebiopsy and for performing the procedure. Patients who did not undergo a rebiopsy, or whose rebiopsy samples were inadequate for testing, transitioned to the treatment states. Multiplexed molecular testing proceeded according to a two-step test sequence: concurrent *EGFR* mutation and ALK overexpression assays followed by ALK FISH confirmation for ALK IHC positive results (1+, 2+, or 3+).[8] Mortality risk in the above health states was modeled based on the natural history of advanced NSCLC for the 'Test-treat' approach, and first-line cisplatin-pemetrexed therapy for the empiric treatment strategies.

Patients in the 'No test' strategy entered the model in the first-line cisplatin-pemetrexed treatment state (Figure 3.1). Upon progression on each therapy, patients transitioned to the next line of therapy based on treatment conditional disease risk of progression. Treatment sequences for the other strategies (Table 3.1) followed the same model structure.

Figure 3.1. Model structure depicting health states and transitions.

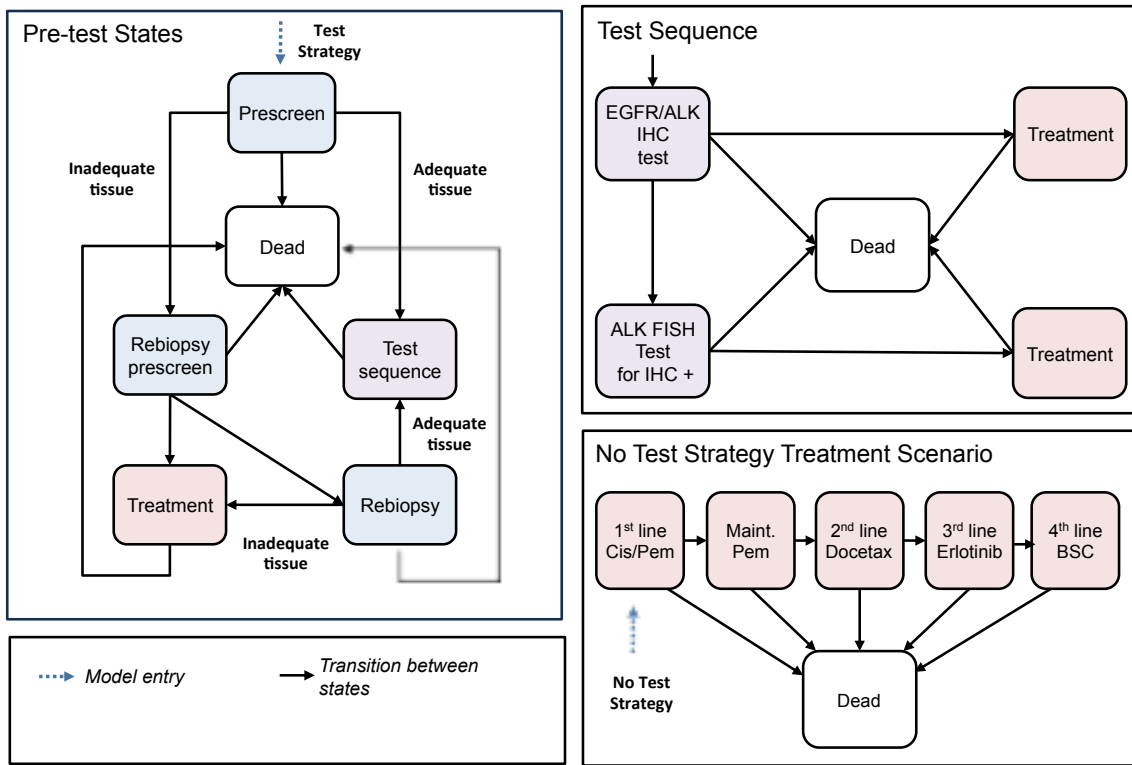


Table 3.1 Strategies.

Strategy	Test	Treatment
No test	None	CisPem* ► Pem ► DTX ► Erlot ► BSC
Empiric therapy[†]	EGFR/ALK IHC ► ALK FISH for ALK IHC 1-3+	Empiric CisPem x 4 cycles ► test result conditional treatment: EGFR +: Erlot ► DTX ► BSC ALK +: Criz ► DTX ► BSC Other: CisPem* ► Pem ► DTX ► Erlot ► BSC
Empiric-switch therapy[‡]	EGFR/ALK IHC ► ALK FISH for ALK IHC 1-3+	Empiric CisPem x 1 cycle ► test result ► test result conditional treatment: EGFR +: Erlot ► CisPem* ► DTX ► BSC ALK +: Criz ► CisPem* ► DTX ► BSC Other: CisPem* ► Pem ► DTX ► Erlot ► BSC
Test-treat	EGFR/ALK IHC ► ALK FISH for ALK IHC 1-3+	EGFR +: Erlot ► CisPem* ► DTX ► BSC ALK +: Criz ► CisPem* ► DTX ► BSC Other: CisPem* ► Pem ► DTX ► Erlot ► BSC

*CisPem therapy was administered for up to 4 cycles; upon progression on CisPem, patients transitioned to the next line of therapy

[†]TKI maintenance treatment was initiated in presence of drug-sensitizing mutations upon completion of 4 cycles of CisPem

[‡]Patients with drug-sensitizing mutations switched to a TKI at time of test results after receiving one cycle of empiric CisPem therapy

Abbreviations: CisPem, cisplatin and pemetrexed doublet; Pem, pemetrexed; DTX, docetaxel; Erlot, erlotinib; BSC, best supportive care; Criz, crizotinib; ALK, anaplastic lymphoma kinase; IHC, immunohistochemistry; FISH, fluorescence in situ hybridization;

For the main analysis, we chose a time horizon of two years to capture the major health and economic consequences in metastatic NSCLC. This duration obviated the need for projecting survival outcomes beyond the primary clinical trial data.[22] Benefits

and costs were discounted at 3% per annum. Analyses were performed in TreeAge Pro 2013 (TreeAge Software, Inc.; Williamstown, MA).

3.3.2. Natural History

We used data from Surveillance, Epidemiology, and End Results (SEER)-Medicare to model the natural history of untreated, metastatic NSCLC for simulated patients who were awaiting molecular test results. Predicted probabilities from a Cox proportional hazards (PH) model for incident SEER cases with Stage IV NSCLC and a pathologic diagnosis of non-squamous histology, aged 66-69 years old with diagnoses between 2007 and 2009, who were managed with BSC were generated. The model was weighted using the inverse conditional probability of exposure to chemotherapy to balance observable covariates between treatment naïve and chemotherapy treated patients. Time dependent transitional probabilities for the simulation model were calibrated to the predicted survival probabilities from the Cox PH model using a piecewise-exponential approach.

3.3.3. Clinical Outcomes

Randomized trials (RCTs) for initiation and maintenance therapy with erlotinib and crizotinib in *EGFR* mutation and *ALK* rearrangement positive patients, respectively, were identified for calculating treatment-conditional progression and survival estimates. Efficacy data for other therapies were pulled from RCTs that enrolled molecularly unselected patients. The trial-based median estimates for treatment-specific overall survival (OS) and PFS were used as calibration targets. Transition probabilities were calculated using a constant hazard assumption.

3.3.4. Quality of Life

We estimated utilities based on a mixed model, which included parameters for best tumor response and toxicities commonly encountered with chemotherapy treatments in NSCLC (neutropenia, febrile neutropenia, fatigue, diarrhea, nausea and vomiting, rash and hair loss).[23] We used rates for best tumor response, and grade 3 and 4 adverse drug events (ADEs) from RCTs to calculate treatment-specific utilities based on the mixed model (Table 3.2).[23] Disutilities for ADEs were incorporated in the first month of therapy.[14, 24]

3.3.5. Genomic Markers

Prevalence rates of biomarkers were drawn from a population-based registry (Table 3.2) of 10,000 NSCLC patients who were enrolled for routine screening of predictive biomarkers.[3] The cumulative TAT for test results is congruent with guidelines, which recommend that EGFR and ALK testing both be completed within 10 working days of receiving the specimen in the laboratory.[8]

We estimated that 30% of patients would undergo a rebiopsy and 85% of repeat biopsies would yield adequate samples for molecular testing.[13] The distribution of repeat biopsy techniques (bronchoscopic, or transthoracic needle aspiration of primary cancer, and metastatic site needle aspirations) and pneumothorax complication rates were based on a prior analysis.[13]

We used ALK FISH positivity as the reference standard for presence of *ALK* rearrangements.[7, 8] Estimates for IHC test performance were taken from the largest published case series evaluating a novel 5A4 monoclonal antibody (Table 3.2). [25]

Table 3.2 Model parameters and ranges for sensitivity analyses.

Variable	Base Case	Low	High	Source
Overall survival, months				
Cisplatin plus pemetrexed	11.8	10.4	13.2	[37]
Pemetrexed	13.9	12.8	16.0	[38]
Docetaxel	8.0	6.4	9.6	[16]
Erlotinib (1 st line)	19.3	14.7	26.8	[39]
Erlotinib (maintenance)*	24.0	19.2	28.8	[40]
Crizotinib	20.3	18.1	26.8	[7]
Erlotinib (3 rd line)	6.7	5.5	7.8	[41]
Best supportive care	4.5	4.3	4.9	SEER-Medicare
Progression-free survival, months				
Cisplatin plus pemetrexed	5.3	4.8	5.7	
Pemetrexed	4.1	3.2	4.6	[37]
Docetaxel	3.3	2.6	4.0	[38]
Erlotinib (1 st line)	9.7	8.4	12.3	[16]
Erlotinib (maintenance)	10.3	8.2	12.4	[39]
Crizotinib	7.7	6.0	8.8	[40]
Erlotinib (3 rd line)	2.2	1.9	2.8	[7] [41]
Health State Utilities				
With best response and adverse events				
Cisplatin plus pemetrexed	0.59	0.51	0.66	[23, 37]
Pemetrexed	0.60	0.54	0.65	[23, 38]
Docetaxel	0.48	0.37	0.59	[16, 23]
Erlotinib (1 st line)	0.64	0.58	0.70	[23, 39]
Erlotinib (maintenance)	0.66	0.61	0.71	[23, 40]
Crizotinib	0.64	0.58	0.70	[7, 23]
Erlotinib (3 rd line)	0.56	0.49	0.64	[23, 41]
No treatment	0.46	0.36	0.55	[23]
With best response and no adverse events				
	0.62	0.56	0.67	[23, 37]
Cisplatin plus pemetrexed	0.60	0.55	0.66	[23, 38]
Pemetrexed	0.57	0.51	0.64	[16, 23]
Docetaxel	0.65	0.60	0.71	[23, 39]
Erlotinib (1 st line)	0.66	0.61	0.71	[23, 40]
Erlotinib (maintenance)	0.66	0.60	0.71	[7, 23]
Crizotinib	0.59	0.53	0.65	[23, 41]
Erlotinib (3 rd line)				
Probabilities (%)				
EGFR mutation positive	9.5	8.9	10.7	[3]
ALK rearrangement positive	3.9	3.5	4.3	[3]
Inadequate tissue – initial biopsy	37.7	26	49	[42]
Re-biopsy	15	10	25	Expert opinion [13]
Inadequate tissue - re-biopsy	96	95	100	[25]
ALK IHC specificity	100	100	100	[25]
ALK IHC sensitivity				

Table 3.2 (continued)

Turnaround time (TAT), days [†]				
With no re-biopsy	12	7	16	[8], Expert Opinion
With re-biopsy	24	13	34	
Costs, 2013 US\$				
EGFR mutation assay	\$201	\$201	\$718	[43, 44]
ALK IHC assay	\$136	\$136	\$217	[43, 44]
ALK FISH assay	\$489	\$489	\$598	[43, 44]
Cisplatin and pemetrexed				
Drug acquisition (per 21 day cycle)	\$5,721	\$4,577	\$6,865	[45]
Premedication	\$254	\$203	\$305	[45, 46]
Administration, monitoring	\$446	\$357	\$535	[43, 44]
Adverse drug event treatment	\$760	\$608	\$912	[43-47]
Pemetrexed maintenance				
Drug acquisition (per 21 day cycle)	\$5,689	\$4,551	\$6,827	[45]
Premedication	\$6	\$5	\$7	[45, 46]
Administration, monitoring	\$276	\$221	\$331	[43, 44]
Adverse drug event treatment	\$304	\$243	\$365	[43-47]
Docetaxel				
Drug acquisition (per 21 day cycle)	\$937	\$750	\$1,124	[45]
Premedication	\$8	\$6	\$10	[45, 46]
Administration, monitoring	\$329	\$263	\$395	[43, 44]
Adverse drug event treatment	\$2,525	\$2,020	\$3,030	[43-47]
Erlotinib				
Drug acquisition (per 21 day cycle)	\$3,982	\$3,186	\$4,778	[46]
Premedication	\$0	\$0	\$0	[45, 46]
Administration, monitoring	\$165	\$132	\$198	[43, 44]
Adverse drug event treatment				
1 st line	\$358	\$286	\$430	[43-47]
3 rd line	\$727	\$582	\$872	[43-47]
Maintenance	\$358	\$286	\$430	[43-47]
Crizotinib				
Drug acquisition (per 21 day cycle)	\$8,041	\$6,433	\$9,649	[46]
Premedication	\$0	\$0	\$0	[45, 46]
Administration, monitoring	\$165	\$132	\$198	[43, 44]
Adverse drug event treatment	\$550	\$440	\$660	[43-47]
Disease progression, per month	\$5,457	\$5,283	\$5,605	[26]
Patient time, per hour	\$19	\$10	\$29	[48]
Travel, per 30 mile round trip	\$15	\$8	\$23	[49]

*probability of survival = 0.6; median survival probability not reported

[†]includes time for delivery of tissue sample to the laboratory

Abbreviations: ALK, anaplastic lymphoma kinase; IHC, immunohistochemistry; FISH, fluorescence in situ hybridization; EGFR, epidermal growth factor receptor; IHC, immunohistochemistry; FISH, fluorescence in situ hybridization; TAT, turnaround time from receipt of specimen to report of test results.

3.3.6. Costs

Cancer-related medical costs, costs of travel and patient time spent seeking medical care were included in the model (Table 3.2). We used the Centers for Medicare and Medicaid Services (CMS) reimbursement rates for each biomarker assay in our base case analysis, and for other direct medical costs, including drug administration, imaging and ADEs. Costs for treatment specific ADEs were assumed to accrue in the first month of therapy.[14, 24] The average sale price (ASP) and average wholesale price (AWP) were used to value injectable and orally administered drugs, respectively. With the exception of cisplatin-pemetrexed chemotherapy, which was administered up to four cycles, patients were assumed to accrue drug-related costs up to the time of progression. Costs for rebiopsy and related complications were derived from the analysis by Handorf, et al.[13] The cost for treating progressive disease was based on lung cancer attributable costs in the last year of life.[26] All costs in the model were adjusted to 2013 values using the GDP deflator series.[27]

3.3.7. Cost Effectiveness Analysis

We calculated the incremental cost-effectiveness by ranking the strategies in order of increasing effectiveness. Strongly dominated strategies, those that had a lower, or equal effectiveness and higher costs, were eliminated. Incremental cost effectiveness ratios (ICERs) were calculated for each strategy in relation to the next best strategy. The ICER is a ratio of the difference in mean costs divided by the difference in mean QALYs. Strategies with a higher ICER that were less effective than

another strategy were eliminated by extended dominance. The ICERs were recalculated for the remaining non-dominated strategies.[28]

3.3.8. Sensitivity Analyses

We conducted sensitivity analyses to evaluate which parameters were most influential on model results. Where available, the ranges used for the parameters corresponded to the 95% CIs (Table 3.2). Costs were varied $\pm 20\%$ and plausible ranges for TATs were used based on expert opinion. We also simulated the lifetime (5 year) costs and effectiveness where prognosis beyond trial observation period was modeled using exponential distributions. Additionally, model outputs were generated based on commercial prices for molecular assays. Finally, we ran a sensitivity analysis for the transition probability of dying while awaiting test results based on treatment naïve patients who were randomized to best supportive care (BSC) in a RCT.[29]

3.4 Results

Multiplexed testing approaches of ‘Test-treat’ and ‘Empiric switch’ were most effective (Table 3.3). Both yielded an average life expectancy of 0.97 life years (LY), and 0.56 QALYs. The ‘Empiric therapy’ approach, in which chemotherapy was continued for four cycles before initiation of molecularly guided therapy, was less effective (0.95 LY and 0.55 QALYs). Because the ‘Empiric switch’ approach was more expensive than the ‘Test-treat’ strategy (but equally effective), it was ruled out by strong dominance. The ‘Empiric therapy’ approach was eliminated by extended dominance since it was associated with a higher ICER than the ‘Test-treat’ approach. Compared with the ‘No test’ strategy, the ‘Test-treat’ approach of concurrent *EGFR* mutation and ALK IHC testing followed by ALK FISH confirmation prior to initiation of any therapy

Table 3.3 Cost Effectiveness Results.

Strategy*	LYs	QALYs	Cost[†]	ICER (\$/LY)	ICER (\$/QALY)
Standard Care: No test, chemotherapy alone	0.93	0.53	\$79,331	-	-
Empiric Therapy	0.95	0.55	\$82,762	Extended Dominance	Extended Dominance
Empiric Switch Therapy	0.97	0.56	\$86,645	Dominated	Dominated
Test-Treat	0.97	0.56	\$83,413	98,000	150,000

Abbreviations: LYs, life-years; QALYs, quality-adjusted life-years; ICER, incremental cost effectiveness ratio;

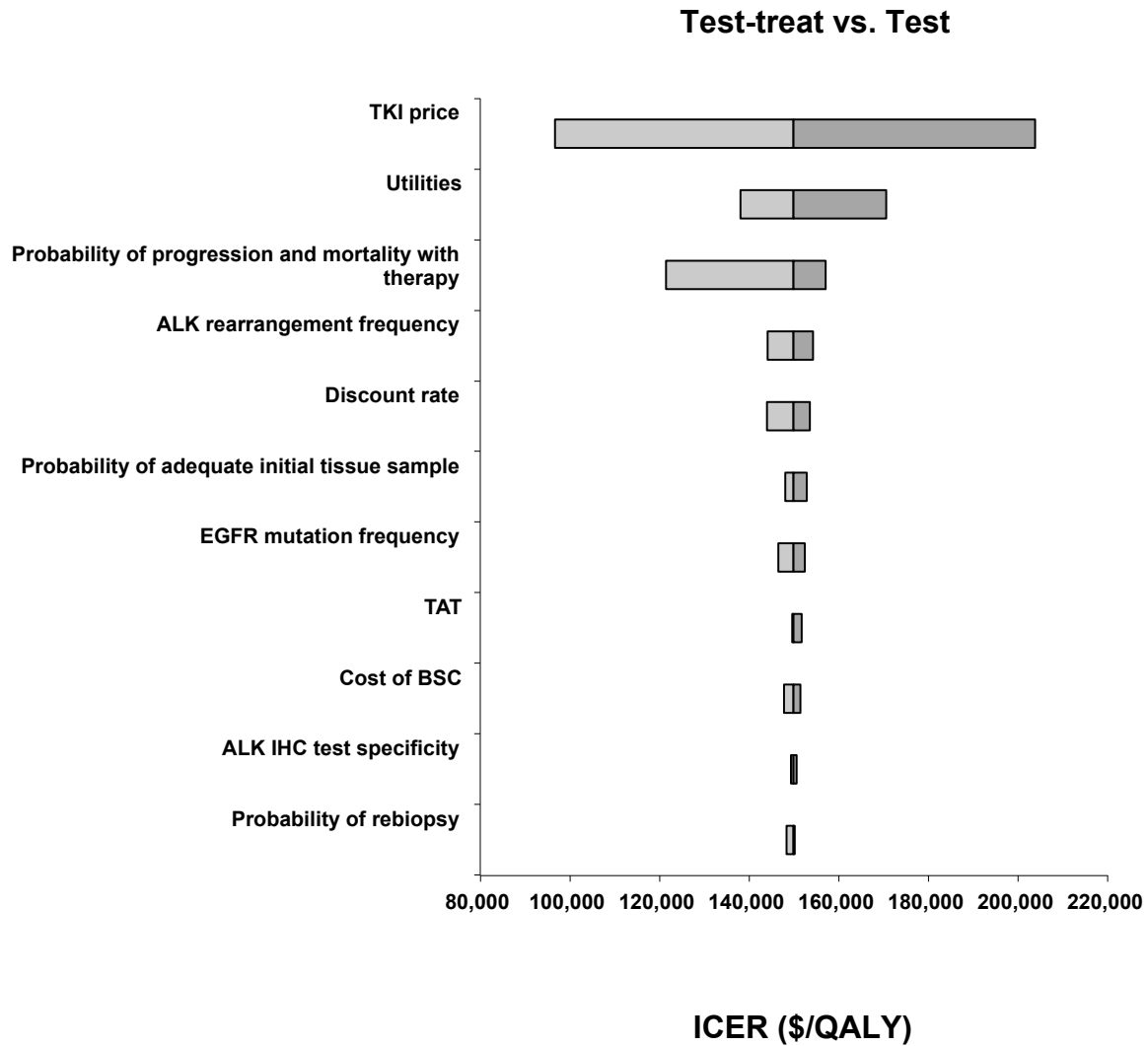
*costs and life expectancy outcomes discounted at 3% annual rate [†]2013 \$US

yielded an ICER of \$150,000 per additional QALY. Without adjustment for quality of life, the ‘Test-treat’ approach had an ICER of \$98,000 per LY gained compared to the ‘No test’ strategy.

3.4.1. Sensitivity Analyses

Changing the parameters values over ranges listed in Table 3.2 did not impact the rank order of the strategies. Also, both empiric treatment strategies remained dominated. A comparison of the non-dominated strategies revealed that the most influential parameters were utilities and acquisition costs for TKIs (Figure 3.2). We found that the ICER for the ‘Test-treat’ approach compared to the ‘No test’ strategy ranged from \$138,000 to \$171,000 per additional QALY, with high and low utility values, respectively; and from \$97,000 to \$204,000 per QALY gained when the TKI acquisition costs were varied by minus and plus 20%, respectively. In all other scenarios, the ICER for ‘Test-treat’ compared to ‘No test’ ranged from \$120,000 to \$160,000 per QALY.

Figure 3.2. Sensitivity analyses. Tornado diagram of influential parameters on the incremental-cost effectiveness ratio (ICER) of 'Test-treat' vs. 'No Test' strategies.



TKI, tyrosine kinase inhibitor; *ALK*, anaplastic lymphoma kinase rearrangement; *EGFR*, epidermal growth factor drug sensitizing mutation; TAT, turn-around time; BSC, best-supportive care; IHC, immunohistochemistry; QALY, quality-adjusted life year.

Commercial prices for assays had a small effect on the ICER (\$167,000 per QALY for the 'Test-treat' vs. 'No test' strategy). Extrapolation of long-term survival lowered the ICER for 'Test-treat' to \$148,000 compared to 'No Test'. With a trial-based mortality risk in the pre-treatment health states (using a piecewise exponential model with survival probabilities of 97% and 90% at 1 and 2 months after diagnosis, respectively), the same dominance pattern was observed and the ICER remained stable for the 'Test-treat' strategy compared to 'No Test' (\$153,000/QALY).[29]

Varying the proportion of patients for whom multiplexed molecular testing is ordered showed that decreasing this proportion to 5%, from 100% in the base-case analysis, would lower the outcomes in terms of expected QALYs to 0.54 for all testing strategies. Both empiric treatment strategies would still be dominated, and the ICER for 'Test-treat' compared to the 'No test' strategy would be \$166,000/QALY.[9]

3.5 Discussion

Concurrent *EGFR* mutation and ALK IHC testing with ALK FISH confirmation for tumors that overexpress the ALK protein prior to initiation of therapy yielded an ICER of \$150,000 per QALY gained compared to no testing and treatment with chemotherapy alone. Whether or not an ICER of \$150,000 provides good value is contingent upon the willingness-to-pay threshold, which serves as a guide of how much society is willing to pay for an additional QALY. The World Health Organization (WHO) defines interventions with ICERs within three times the GDP per capita as being cost effective (\$155,000 in the US). [30] Others posit that a threshold of \$200,000 per QALY may be more appropriate based on empirical data of ICERs for commonly used interventions.[31, 32] Using these benchmarks, our results suggest that multiplexed

testing followed by molecularly guided therapy in metastatic NSCLC provides good value from a societal perspective.

Our simulation study confirms that waiting for test results prior to initiation of treatment optimizes outcomes in newly diagnosed patients with metastatic NSCLC.[10]

While empiric therapy in which chemotherapy is initiated concurrently with testing for mutations, followed by an immediate switch to molecularly guided therapy at the time test results become available yielded the same life expectancy as the test then treat approach, the former strategy was dominated since it was more expensive.

Continuation of empiric chemotherapy for four cycles before switching to test-result conditional treatment yielded less favorable outcomes than the above two approaches, both in terms of QALYs and LYs. This strategy was eliminated by extended dominance. These results were robust to variations over plausible ranges of model parameters.

In sensitivity analyses, the ICER was highly sensitive to drug acquisition costs. At lower TKI prices, (80% of brand name product price), the ICER for the 'Test-treat' strategy decreased to \$97,000/QALY compared to standard treatment with chemotherapy. Over time, once generic versions of TKIs become available, these innovations will confer even better value. The optimal price point that maximizes social welfare, while minimizing the impact on technological innovation, is outside the scope of this analysis. However, growing concerns over the increasing cost burden of these innovations on patients deserve scrutiny.[33-35] Patient access to these drugs may be impeded by onerous out of pocket costs. One way to attenuate the impact of cost sharing may be through value based benefit design. Arguably, breakthrough therapies that offer substantial improvement in outcomes and are placed into lower cost sharing

tiers would benefit society as a whole from healthier patients who remain productive, as they are able to access these beneficial treatments.

We were unable to identify published economic analyses that examined multiplexed testing in advanced NSCLC. Handorf, et al. evaluated the cost effectiveness of molecularly guided first-line therapy using *EGFR* mutation testing in the US from a payer perspective. The ICERs for testing with and without rebiopsy and *EGFR* mutation guided treatment ranged from \$110,644 to \$122,219 per QALY gained compared to treatment with a carboplatin-paclitaxel doublet.[13] Similar to our analysis, the cost-effectiveness results from that study support the value of molecularly guided therapy. Another recently published study examined the cost-effectiveness of *ALK* rearrangement testing alone prior to first-line crizotinib treatment in *ALK*-positive tumors or cisplatin-gemcitabine combination chemotherapy in wild type tumors.[21] From a Canadian public health perspective, that analysis generated an ICER of \$255,970 per additional QALY for molecularly guided therapy compared to chemotherapy. The authors concluded that genetic testing and treatment with molecularly guided therapy was not cost-effective. Several differences between our analysis and the Canadian study are worth noting. First, we combined multiplexed testing in our analysis, which de facto produces better outcomes for the molecular testing strategy since more patients benefit from testing. Second, in our analysis, the mean life expectancy with doublet chemotherapy using a lifetime horizon was 12.2 months, an estimate that is identical to a separate analysis we conducted based on SEER-Medicare patients with newly diagnosed Stage IV NSCLC (data not shown). On the other hand, Djalalov et al. reported a mean life expectancy of 7.4 months in patients who initiated therapy with

first-line cisplatin and gemcitabine.[21] Third, our utility weights were appreciably higher for crizotinib and some other overlapping treatments, such as third-line erlotinib therapy. These differences in part explain the disparities in our respective studies.

Our results are subject to modeling assumptions and need to be interpreted in this context. For example, due to treatment crossover after progression and lack of direct comparisons in RCTs, we relied on single-arm data for our parameters. Furthermore, we used data from PROFILE 1007, a phase 3 RCT of second-line crizotinib, to inform hazard rates in our model for OS and PFS.[7] These estimates apply to a small subset of patients in our model, those with *ALK* rearrangement positive status. Any bias introduced into the model would thus be marginal given the size of this subgroup.[36] Overall, varying the hazard rates for treatment effects in sensitivity analyses revealed that the base case results were robust to these assumptions. Also, we used Medicare reimbursements as a proxy for the societal costs of test assays. However, the true costs of the tests may vary across providers. But even with commercial test prices, the ICER for the ‘Test-treat’ compared to the ‘No test’ strategy increased to \$167,000 per additional QALY, which is still below commonly acceptable willingness-to-pay thresholds.[31]

In summary, our analysis suggests that multiplexed testing for *EGFR* mutations and *ALK* overexpression with an IHC assay followed by *ALK* rearrangement confirmation with FISH for IHC positive results and biomarker conditional treatment is a cost effective strategy compared to treatment with chemotherapy and no testing in metastatic NSCLC. Empiric cisplatin-pemetrexed therapy for four cycles with concurrent molecular testing prior to initiation of TKI maintenance therapy generated

inferior outcomes compared to waiting for test results before treatment, and compared to 'Empiric switch therapy' in which chemotherapy initiated treatment was immediately switched to molecularly guided therapy when test results became available.

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3.7 Appendix

3.7.1 Natural History

To model the natural history of untreated advanced NSCLC while simulated patients were awaiting molecular marker test results and for those in the BSC strategy, we used the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database to identify incident cases of advanced NSCLC patients with pathologic diagnosis of non-squamous histology, aged 66-69 years old, who were diagnosed between 2007 and 2009. The SEER population-based registries, which represent 28% of the US population, provide a rich repository of data related to tumor characteristics and prognosis.[7] The patient-level linked Medicare data (CMS) provide claims information for fee-for-service (FFS) coverage for services provided in hospitals, outpatient clinics, physician encounters, durable medical equipment, hospice, home health care and prescription medications covered by Medicare Part D plans. We used predicted probabilities from a Cox model probability weighted using the inverse conditional probability of exposure to systemic therapy to balance observable covariates between treatment naïve and treated patients. Time dependent transitional probabilities for the simulation model were calibrated to the predicted survival probabilities from the Cox model using a piecewise-exponential approach.

Patients with Stage IV NSCLC who were diagnosed during 2007-2009 were identified from the SEER database. Further inclusion criteria included: age 66 to 69 (the ages were selected to parallel the median ages reported in the clinical trials which were used for treatment efficacy estimates); non-squamous histology (adenocarcinoma, large cell, NOS; BAC histology was excluded from the analysis); first and only cancer

diagnosis; continuous enrollment in FFS. The minimum follow up was 12 months after diagnosis. Classification into the systemic treatment group was based on any claim for systemic therapy (in hospital, physician, outpatient, Medicare D, home health care and durable equipment claims files) within 60 days of diagnosis. To ensure that patients included in the analysis were representative of those who would be candidates for systemic therapy, we matched patients based on 39 characteristics, which included proxy indicators for performance status at diagnosis (2 variables: claims for home oxygen therapy and claims for activity of daily living aids). (We would like to thank Dr. Lamont for providing us with the algorithm for the performance status indicators).

A propensity score logistic regression model was estimated, using receipt of systemic therapy as the outcome variable and the above variables that may affect treatment selection as the covariates. Inverse propensity score weighting (IPW) was used to assess the balance in baseline characteristics. All standardized differences for IPW weighted analyses of each covariate between the treatment groups were less than 0.10 indicating the groups were well balanced on baseline characteristics (Table 3.A.1) across treatment groups among the 11,443 included patients.

Table 3.A.1. Baseline characteristics among Stage IV NSCLC patients by treatment group.

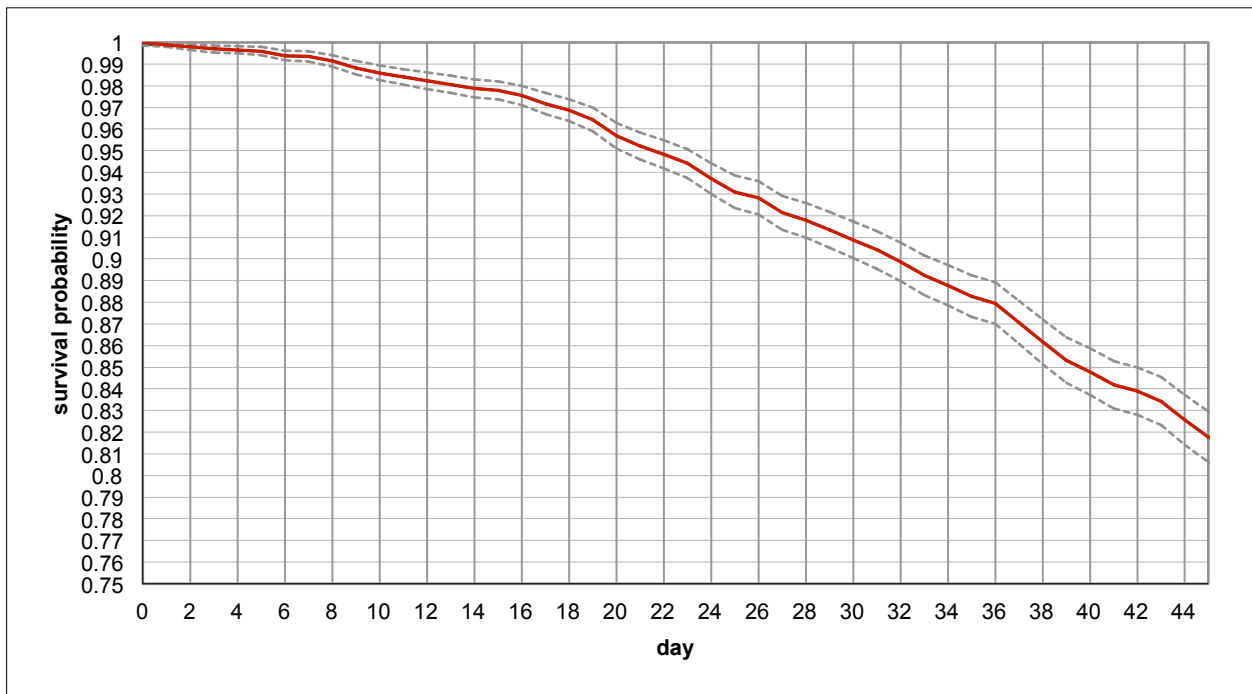
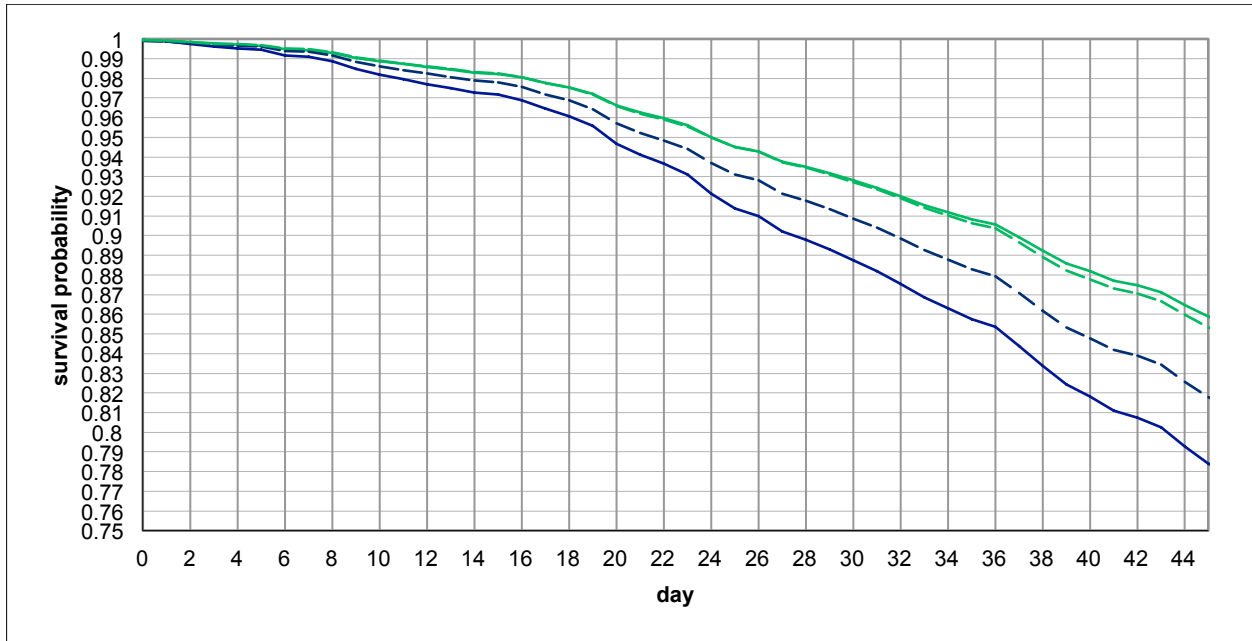
	Unweighted means			Weighted means		
	Systemic therapy N=5050 %	BSC N=6393 %	Standardized Difference	Systemic Therapy N=5050 %	BSC N=6393 %	Standardized Difference
Female	48	51	0.057	50	50	0.001
Age						
66-69	25	17	0.208	21	20	0.004
70-74	30	23	0.171	26	26	0.006
75-79	25	23	0.035	24	24	0.001
80-84	15	21	0.154	18	18	0.003
85+	5	16	0.381	11	11	0.006
Race						
Hispanic	4	4	0.017	4	4	0.004
White	82	80	0.050	80	80	0.005
Black	7	9	0.081	8	8	0.003
Other race	8	7	0.023	8	7	0.008
Marital status						
Single	7	9	0.060	8	8	0.005
Married	58	44	0.284	51	51	0.000
Unknown	35	47	0.255	42	41	0.003
Median household income in census tract	\$50,515	\$48,105	0.107	\$49,067	\$49,066	0.000
Proportion with college degree in census tract	25.3	24.1	0.072	24.5	24.6	0.047
Gagne comorbidity score						
0	67	59	0.184	62	62	0.012
1	16	17	0.035	17	17	0.000
2	8	9	0.038	8	8	0.000
3+	9	15	0.201	13	12	0.018
Histology						
Adenocarcinoma	56	56	0.004	56	56	0.003
Large cell	5	5	0.020	5	5	0.000
BAC	2	2	0.001	2	2	0.002
NOS	37	37	0.013	37	37	0.003
Brain metastases	16	21	0.137	19	19	0.002
MDs in county, (per 100,000)	238.5	240.1	0.012	238.1	239.5	0.081
Hospital beds in county, (per 100,000)	320.9	322.2	0.006	323.7	320.2	0.131
Managed care penetration (%)	19.7	20.6	0.071	20.2	20.3	0.020
Foreign born (%)	13.0	12.9	0.009	13.0	12.9	0.038
Hospital days pre dx	3.0	4.8	0.224	4.3	4.1	0.108
Home health care enrolment pre dx	8	14	0.217	12	11	0.021
SNF enrolment pre dx	3	8	0.233	6	6	0.002
Pre-diagnosis costs, within 1 year of diagnosis, mean (SD)	\$6,884	\$10,053	0.172	\$8,985	\$8,752	0.080
State buy-in	16	21	0.133	19	19	0.004
Alcohol abuse	0	1	0.037	1	1	0.000
CHF	9	13	0.136	11	11	0.016
Cardiac arrhythmias	11	15	0.115	14	13	0.014
Chronic pulmonary disease	22	25	0.083	24	24	0.009
Coagulopathy	2	2	0.005	2	2	0.014
Complicated diabetes	5	6	0.048	6	6	0.008
Deficiency anemias	11	14	0.089	13	12	0.009
Dementia	1	3	0.153	2	2	0.007
Fluid and electrolyte dis	4	8	0.140	7	6	0.012
HIV/AIDS	0	0	0.003	0	0	0.008
Hemiplegia	0	1	0.064	0	0	0.005
Hypertension	53	52	0.023	53	52	0.010
Liver disease	13	15	0.037	14	14	0.009
Peripheral vascular disor	11	15	0.129	13	13	0.011
Psychosis	2	3	0.077	3	2	0.005
Pulmonary circulation dis	1	2	0.043	1	1	0.001
Renal failure	4	7	0.123	6	6	0.013
Weight loss	0	1	0.092	1	1	0.031
COPD ER/hosp prior to diagnosis	2	3	0.081	2	2	0.011
Home Oxygen Therapy Aids	15	18	0.076	18	17	0.016
ADL Aids	7	11	0.141	10	10	0.016

3.7.2 Survival Analysis

Non-parametric Kaplan-Meier survival curves are useful in characterizing the survival function and do not require any distributional assumptions, however, adjustment for confounding using IPW is not feasible with this approach. We thus pursued both semi-parametric models (Cox model) and parametric models (exponential, Weibull, generalized gamma, log-logistic and log-normal) to adjust for IPW. Models were fit with treatment indicator as the sole covariate and weighted using the IPW. All models were analyzed using SAS (version 9.3). Goodness-of-Fit statistics using the corrected Akaike information criterion (AICc) were used to compare the fit of the hazard function across models. The Cox model was associated with the lowest AICc value and was thus deemed to have the best fit to the data.

Furthermore, to attenuate survivor treatment selection bias, we opted to express the treatment variable as a time-dependent covariate in the Cox PH model. (6) The predicted survival probabilities from the Cox PH models and the calibrated probabilities from the simulation model are shown below. Time dependent transitional probabilities for the simulation model were calibrated to the Cox predicted survival probabilities using a piecewise-exponential approach.

Figure 3.A.1. Natural history model calibration.



Top panel: The overall predicted survival probabilities from Cox PH models for systemic therapy and treatment naïve groups (green and blue lines, respectively) are shown. Predictions from separate specifications of Cox PH models are shown: solid lines correspond to estimates with treatment as a fixed covariate; dashed lines correspond to time-varying treatment covariate specification. Bottom panel: Red curve represents the calibrated survival probability curve from the simulation model; dashed blue line corresponds to the predicted survival probabilities for treatment naïve group with chemotherapy as a time-varying covariate; grey curves correspond to the 96% CI. All Cox PH model results are inverse probability weighted for propensity to receive systemic therapy within 60 days from diagnosis.

3.7.3 Treatment Conditional Outcomes

The model simulated progression-free and overall treatment conditional survival using exponential models. Studies that met inclusion criteria for estimation of these efficacy parameters comprised of phase 3 randomized trials. With the exception of first-line crizotinib and switch maintenance erlotinib, we were able to identify studies for all other lines of treatment that met the inclusion criteria. The PROFILE 1007 trial evaluated the efficacy of crizotinib in the second line treatment.[9] The PROFILE 1014 trial is currently enrolling patients in the first line setting, but the results will not be available for some time (personal communication, Dr. Shaw). There is an ongoing debate about the consistency of outcome results with targeted therapies between first and second line therapy given no direct comparisons of the two approaches.[10] Indirect comparisons suggest relatively better outcomes in first line setting compared to second line, but the evidence is based on retrospective analyses or small sample sizes. The use of PROFILE 1007 results in the first line setting in our model applies to a small subset of patients with ALK rearrangement positive status (<5%). Any bias introduced into a model would thus be marginal given the size of the subgroup and it would be in favor of the standard care strategy.

The median estimates from trials were used as the calibration targets. The hazard rates were changed iteratively to approximate the arm-specific median survival estimates from eligible trials.

Table 3.A.2. Calibration results of simulation model parameters compared with randomized trials.

Variable	Trial	Simulation
Overall survival, months		
Cisplatin plus pemetrexed	11.8	11.8
Pemetrexed	13.9	13.9
Erlotinib (1st line)	19.3	19.3
Erlotinib (maintenance)	24.0	23.8
Crizotinib	20.3	20.2
Erlotinib (3rd line)	6.7	6.6
Docetaxel	8.0	7.9
Best supportive care (4th line)	4.6	4.6
Progression-free survival, months		
Cisplatin plus pemetrexed	5.3	5.3
Pemetrexed	4.1	4.1
Erlotinib (1st line)	9.7	9.6
Erlotinib (maintenance)	10.3	10.3
Crizotinib	7.7	7.6
Erlotinib (3rd line)	2.2	2.2
Docetaxel	3.3	3.4

Figure 3.A.2. Calibration of treatment conditional survival curves.

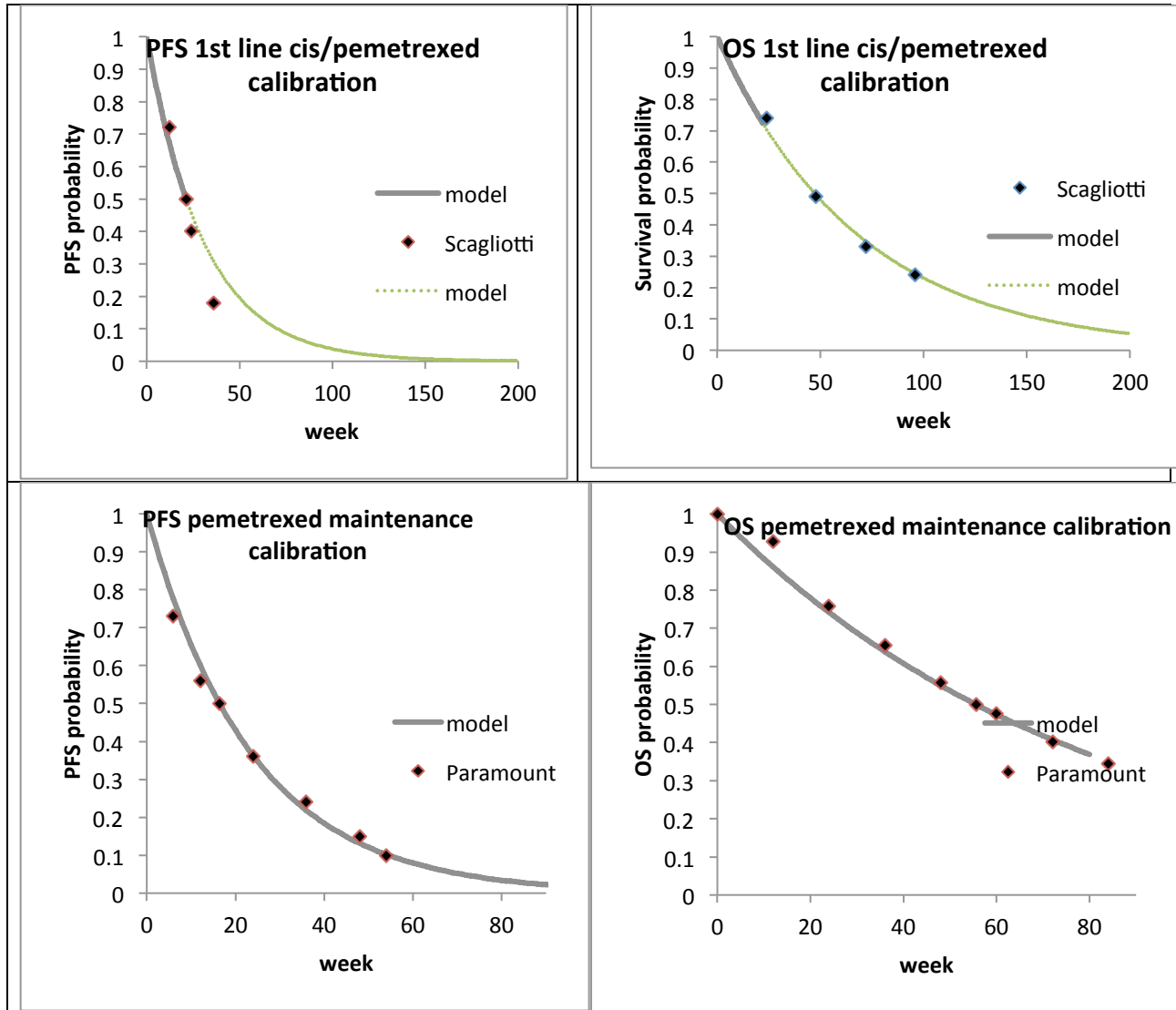


Figure 3.A.2. (continued)

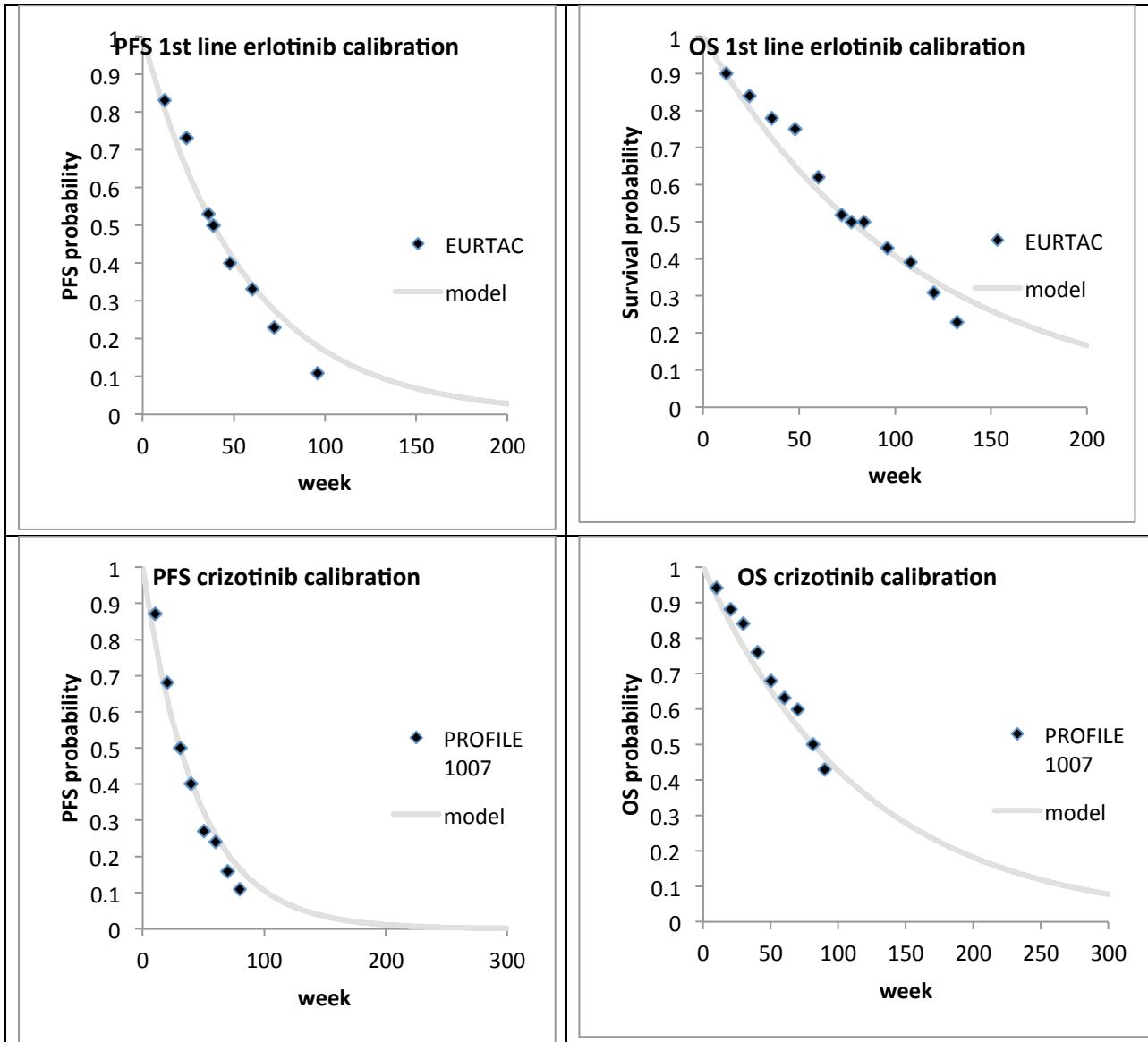
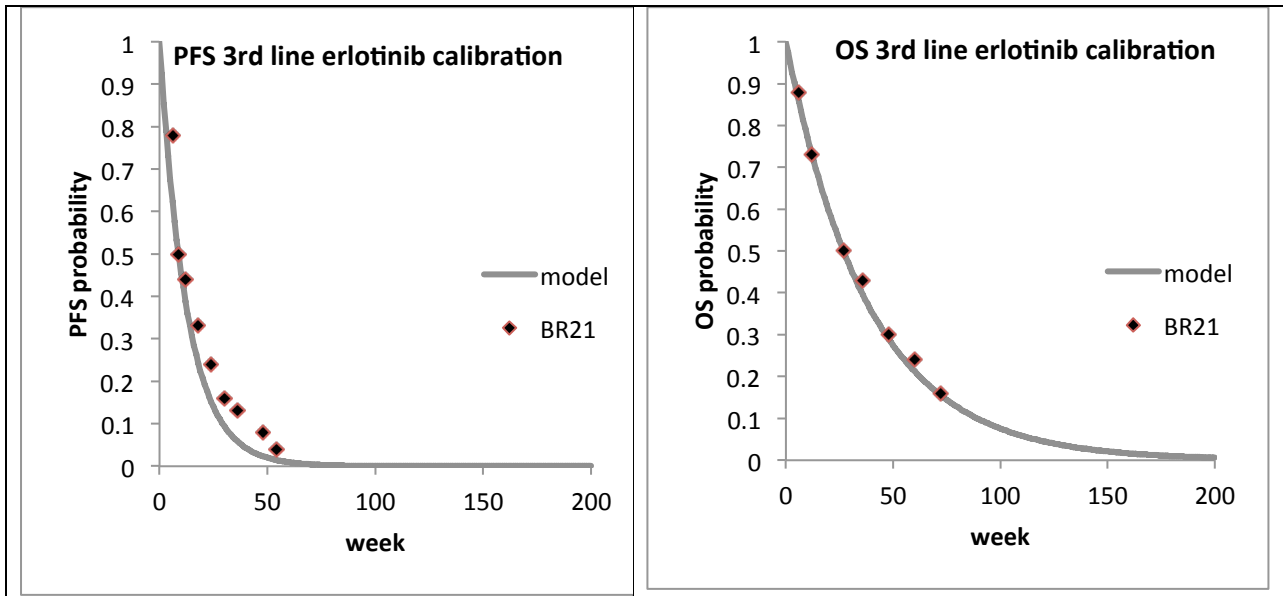


Figure 3.A.2. (continued)



Model predicted survival probabilities (grey curves) are juxtaposed with survival probabilities from randomized clinical trials included in the model (diamonds). Non-solid curves correspond to model predictions that extend beyond the analytical time.

3.7.4 Best Response and Adverse Drug Event Rates

Best response rates (CR/PR, SD, PD) were pulled from the randomized trials that we included for efficacy endpoints. Prevalence of grade 3 and 4 adverse drug events (ADE) were obtained from the same trials (Table 3.A.3). ADE and best response frequencies were assumed to be fixed in our model.

Table 3.A.3. Best response and adverse event probabilities by treatment.

	Therapy*	Erlotinib 1st line	Crizotinib	Erlotinib maintenance	Cisplatin/pemetrexed	Pemetrexed	Erlotinib 3rd line	Docetaxel
	Source	EURTAC	PROFILE	SATURN	Scagliotti	PARAMOUNT	BR21	meta
Best response	CR/PR**	0.58	0.66	0.55	0.31	0.03	0.09	0.09
	PD**	0.07	0.06	0.00	0.23	0.28	0.38	0.46
Grade 3/4 ADE	Neutropenia	0.00	0.13	0.00	0.15	0.04	0.00	0.32
	Febrile Neutropenia	0.00	0.01	0.01	0.01	0.01	0.00	0.06
	fatigue	0.06	0.02	0.00	0.07	0.04	0.16	0.28
	N&V	0.00	0.02	0.00	0.13	0.01	0.00	0.26
	diarrhea	0.05	0.00	0.02	0.00	0.00	0.11	0.12
	hair loss	0.00	0.00	0.00	0.12	0.00	0.00	0.38
	rash	0.13	0.00	0.09	0.00	0.00	0.16	0.07

3.7.5 Utilities

Treatment specific utilities were calculated based on the prediction model reported by Nafees et al. (Table 3.A.4).[11] Time spent in each health state was weighted by a utility for that state to estimate QALYs. Utilities were drawn from a community-based study in advanced NSCLC from the UK.[11] The authors elicited societal based utility values from 100 participants of the general community using the standard gamble approach. The predictive model for health state utilities generated by the authors is shown in Table 3.A.4. The model was a function of tumor progression

state (CR/PR, SD, PD) and grade 3-4 toxicities associated with treatment (neutropenia, febrile neutropenia, fatigue, diarrhea, nausea and vomiting, rash and hair loss), domains which demonstrated an impact on HRQOL in prior studies. We calculated utilities based on the Nafees model and trial-based best response rates (CR/PR, SD, PD) and prevalence rates of grade 3 and 4 adverse drug events (ADEs) (Table 3.A.3). ADE and best response frequencies were treated as fixed values. Consistent with other reports, disutilities for ADEs were incorporated for the first month of therapy while remaining months on therapy were weighted using weights calculated using best response rates only.[12] All patients in the BSC health state were assumed to be in the progressive state with no additional disutilities based on symptoms.

Table 3.A.4. Predictive model of utilities in lung cancer based on best response to therapy and adverse events.

Utility	Base case estimate	Standard error	Source
Intercept	0.6532	0.02223	Nafees 2009
PD	-0.1798	0.02169	Nafees 2009
CR/PR	0.0193	0.006556	Nafees 2009
Neutropenia	-0.08973	0.01543	Nafees 2009
FN	-0.09002	0.01633	Nafees 2009
Fatigue	-0.07346	0.01849	Nafees 2009
N&V	-0.04802	0.01618	Nafees 2009
Diarrhea	-0.0468	0.01553	Nafees 2009
Alopecia	-0.04495	0.01482	Nafees 2009
Rash	-0.03248	0.01171	Nafees 2009