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RAPID COMMUNICATION

Cost of early progression: patients with epidermal growth factor receptor mutated metastatic non-small-cell lung cancer

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ABSTRACT

Aim: Compare healthcare costs for patients with epidermal growth factor receptor mutated (EGFRm) metastatic non-small-cell lung cancer (mNSCLC) with and without progression and estimate costs of progression.

Materials & methods: Retrospective claims analysis (2015–2020) from adults with EGFRm mNSCLC initiating EGFR tyrosine kinase inhibitors. Adjusted costs for 12 months were compared (with vs without progression) and cumulative costs for early versus late progression were predicted over 36 months.

Results: A total of 228 patients with EGFRm mNSCLC were included. Patients with progression within 12 months incurred significantly higher total costs despite lower treatment costs (vs without progression). Medical costs were significantly higher among early versus late progressors.

Conclusion: These data may aid providers aiming to administer quality care in a cost-efficient way.

PLAIN LANGUAGE SUMMARY

Lung cancer is the leading cause of cancer death among both men and women in the US. Among US patients with adenocarcinoma histology, approximately 17% have epidermal growth factor activating mutations (EGFRm) that include exon 19 deletions or L858R mutations. These common mutations make up approximately 85% of all EGFR mutations. The aim of this study was to compare healthcare resource utilization and costs for patients with EGFRm metastatic non-small-cell lung cancer with and without disease progression within the first 12 months following first-line treatment initiation using data from insurance claims. The results suggest that patients with EGFRm metastatic non-small-cell lung cancer with disease progression in the first 12 months (after treatment initiation) have significantly higher costs compared with patients without disease progression in the first 12 months (and highest in the first 6 months). These data may help inform oncology providers aiming to administer high quality cancer care in a cost-efficient way.

1. Background

Lung cancer is the leading cause of cancer death among both men and women in the US [1]. Of patients with non-small-cell lung cancer (NSCLC), more than half are diagnosed after the disease has metastasized, and their 5-year survival rate is estimated to be approximately 5% [2]. Among US patients with adenocarcinoma histology, approximately 17% have epidermal growth factor activating mutations (EGFRm) that include exon 19 deletions or L858R mutations. These common mutations make up approximately 85% of all EGFR mutations [3–6].

The recommended first-line treatment for patients with common EGFR mutations include the EGFR-targeted tyrosine kinase inhibitors (TKI) osimertinib, erlotinib, afatinib and gefitinib which have been shown to extend progression-free survival (PFS) when compared with a platinum doublet [7–10]. However, most patients eventually develop resistance to targeted therapies and upon disease progression, subsequent treatment with systemic chemotherapy is recommended [1,11].

Metastatic NSCLC (mNSCLC) is not only burdensome for the patient, but also the healthcare system. Cancer treatment and care is the fastest growing healthcare sector in the US, and it is estimated that lung cancer has the highest last year of life costs [10,12,13]. In a study of patients with mNSCLC, costs in patients with progression were significantly higher compared with similar patients with stable disease, and the authors noted that these incremental costs affect healthcare bud-

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gets within a short period of time postprogression [14]. In a more recent study using data through 2014, the incremental costs of metastatic lung cancer progression were estimated over 3 years and varied markedly by the period of time elapsed prior to progression. Patients who progressed in the first month had costs 82.1% higher than nonprogressors, compared with 28.0% higher costs in patients who progressed in month 24 versus non-progressors [15]. These data highlight the benefits of delaying disease progression, although data examining the economic impact of progression are limited.

The current analysis uses Real World Data to expand on prior research by focusing specifically on an EGFRm mNSCLC population who received targeted therapy as first-line treatment. In addition, we utilize more recent data (January 2015 through December 2020) to capture the current treatment paradigm and reflect increased oncology costs. The aim of this study was to compare healthcare resource utilization (HCRU) and costs for patients with EGFRm mNSCLC with and without disease progression within the first 12 months following first-line treatment initiation and to estimate the incremental costs of early (months 0–12) and late progression (13–36) for up to 36 months after first-line treatment initiation.

These data will increase understanding on the total cost of care in this targeted lung cancer population and how delaying disease advancement may impact medical costs.

2. Materials & methods

2.1. Study design & data source

This retrospective study utilized US administrative claims data from the Merative MarketScan® Commercial Claims and Encounters and Medicare Supplemental and Coordination of Benefits (Medicare) Databases [16]. The databases include the inpatient, outpatient and prescription drug experiences of employees, dependents and retirees covered under a variety of fee-for-service and managed care health plans. Additionally, the National Death Index (NDI) database from the National Center for Health Statistics was linked to the MarketScan databases. The NDI data include all deaths in the US from 1979 forward and provide dates and cause(s) of death for persons who have died. Institutional Review Board (IRB) waiver of authorization approval was obtained from WCG IRB (IRB study #: 1324891; IRB protocol #: 20217016) on 23 December 2021. All variables were defined using International Classification of Diseases, 9th and 10th Revision, Clinical Modification (ICD-9-CM and ICD-10-CM) codes, Current Procedural Terminology 4th edition (CPT-4) codes, Healthcare Common Procedure Coding System (HCPCS) codes and National Drug Codes (NDCs).

2.2. Patient selection

Patients (age 18+) with an eligible diagnosis of lung cancer (two nondiagnostic medical claims at least 30 days apart with an ICD-9-CM [162.2–162.9] or ICD-10-CM [C34.x] code for the condition) during 1 January 2015 through 31 December 2020, were initially selected. Patients were further required to have at least one medical claim with a diagnosis code for secondary malignancy suggesting the presence of metastatic disease (ICD-9: 196.x-198.x; ICD-10: C77.x-C79.x) during the 30 days prior or anytime following the earliest lung cancer diagnosis date (first claim was defined as the metastatic lung cancer diagnosis date). Patients were required to initiate first-line treatment with erlotinib, afatinib, gefitinib, dacomitinib or osimertinib monotherapy (index date) on or following the metastatic lung cancer diagnosis date. Use of an EGFR TKI was also used as a proxy identifier for common EGFR mutations (i.e., exon 19 deletion or L858R mutation) and non-small-cell histology.

Eligible patients were required to have continuous enrollment with medical and pharmacy benefits from index date for a minimum of 60 days following the index date (except if a death). The follow-up period was variable in length until death, database disenrollment, a maximum of 36 months, or study end (31 December 2020) (Figure 1). Patients with evidence of other primary cancers (not including lung) during the 6 months prior to diagnosis of metastatic disease (baseline period) through the day prior to index were excluded. Patients were excluded if they had any claims for the prescription or administration of any systemic antineoplastic therapy (other than the index EGFR TKI) from the metastatic diagnosis date to the day prior to the index date. The final cohort included eligible patients with linkage to the NDI.

Demographic characteristics were reported on the index date and included age, sex, payer and index year. The National Cancer Institute (NCI) adapted Charlson Comorbidity Index [17] calculated as an aggregate measure of patient comorbidity was measured during the baseline period and first line EGFR-TKI drug type was reported on the index date.

2.3. Disease progression

A treatment-based claims algorithm was applied to identify antineoplastic lines of therapy (LOT) after the metastatic lung cancer diagnosis date. Combination regimens were defined as any new drug that was filled/administered within 45 days of a previous drug fill or administration. Termination of a LOT was defined as the discontinuation of all agents in a regimen for ≥60 days, or when a new agent was added (triggering advancement
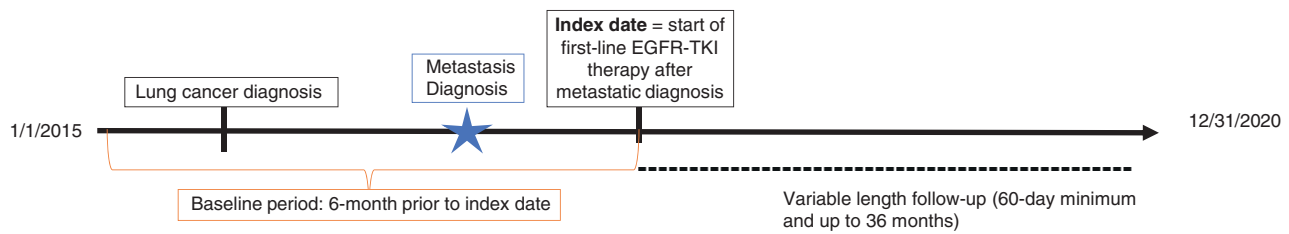
Figure 1. Study design.
EGFR: Epidermal growth factor receptor; TKI: Tyrosine kinase inhibitor.

to a new LOT). A switch between chemotherapy agents within the same medication class did not advance the LOT. Moving to a next line therapy was defined the introduction of a new agent (that was not included in the prior LOT). Disease progression was defined as advancing to a next line of therapy, having medical claims with evidence of hospice care, or death. If multiple events occurred during follow-up, the date of progression was set to the date of the earliest event. Time to first progression was calculated from index date to the earlier of progression (among those with progression). Follow-up was censored at disenrollment or end of study period (among those without progression). The progression triggering event (advancement to a subsequent line of therapy, hospice care or death) was reported. Patients with progression at anytime during follow-up were stratified by early (months 0–12 for first progression triggering event) and late progression (months 13–36 for first progression triggering event).

2.4. Outcomes

Healthcare costs were identified based on paid amounts of adjudicated claims, including insurer and health plan payments as well as patient cost-sharing in the form of copayment, deductible and coinsurance. All dollar estimates were inflated to 2020 dollars using the Medical Care Component of the Consumer Price Index. HCRU and costs were measured per-patient per month (PPPM) during the first 12 months of follow-up for patients with and without progression (stratified by those with progression during months 0–6 and months 7–12). HCRU and costs were reported by type of service (inpatient, outpatient [emergency room, office administered treatment, office visits, laboratory, radiology inclusive of diagnostic and therapeutic radiology services, other] and pharmacy). In addition, healthcare costs were evaluated with and without the costs of antineoplastic treatment (both medical and pharmacy treatment costs).

2.5. Statistical analysis

Descriptive analyses were conducted using the latest version of World Programming System, which is a software platform for working with data and statistics. Categorical variables were presented as the count and percentage of patients in each category, and continuous variables were summarized by mean and standard deviation (SD). General linear regression models were used to adjust PPPM costs for patients with versus without disease progression during the first 12 months post index.

Weighted marginal effects generalized estimating equations (GEE) (normal distributions with identity link) with robust standard errors adjusting for within patient correlations over month for the patient level parameter estimates were used to predict adjusted cumulative monthly costs (total, medical and antineoplastic) for patients with early vs late progression over 36 months. The GEE model was utilized as it provides individual month costs (allowing for a clearer graphical representation of the data) for each month and extending out over 36 months over a more simplified regression model that provides a single estimate of cumulative costs at 36 months. The individual patient's weights were calculated as the inverse of the probability of disenrollment for a patient's month of disenrollment. Post the fitting of the GEE model, cumulative observed and predicted monthly costs were calculated from the summed observed and predicted (from the fitted model) monthly costs.

Baseline covariates included in all adjusted analyses (to account for known potential confounding of the relationship between healthcare costs and disease progression) were: age, sex, region, insurance plan type, urbanicity, payer type, index year, NCI score and first-line TKI drug type. Diagnostics were assessed to examine the variance inflation factor to measure the impact of collinearity among the variables included in the models. All variables had a variance inflation factor of 1–4 suggesting no to moderate correlation and therefore coefficient estimates and p-values estimates in the regressions are reliable.

3. Results

3.1. Patient characteristics

There were 286 patients with EGFRm mNSCLC who met the study eligibility criteria and of those 228 (79.7%) were linked to the NDI and comprised the final sample for analysis (Figure 2). After first-line EGFR-TKI initiation, there were 152 (66.7%) patients with disease progression during follow-up, with a mean (SD) time to progression of 311.1 (219.2) days. Of the patients with progression (n = 152), 66.4% (n = 101) progressed early (first 12 months) while 34.2% (n = 51) progressed late (13–36 months). The mean number of LOT during follow-up was 2.2 (median 2.0) for both early and late progressors. Among patients with progression in the first 12 months (n = 101) 59.4% progressed due to line of therapy advancement, followed by 24.8% having hospice care and 15.8% with death. Patients who progressed most quickly in months 0–6, had a larger proportion with progression due to hospice and death (32.6 and 17.4% respectively, versus those who progressed in months 7–12 (18.2% with hospice and 17.4% with death Figure 3).

In the full cohort, mean (SD) age was 63.0 (12.4) years, 66.2% were female, and the mean (SD) NCI score was 0.4 (0.4). The average duration of follow-up was 551.0 days and was shorter for patients with (without) disease progression in the first 12 months (444.5 vs 563.9 days, $p = 0.004$ Table 1). The most common EGFK-TKI prescribed in first-line was erlotinib (43.4%, n = 99), followed by osimertinib (33.8%, n = 77), afatinib (21.5%, n = 49) and gefitinib (1.3%, n = 3 Table 1). Patients initiating treatment on erlotinib or afatinib were more likely to progress during the first 12 months (58.6 and 46.9%) compared with patients starting their first-line of therapy with osimertinib (26.0% Figure 4).

3.2. Healthcare resource utilization & costs

Patients with progression in the first 12 months of follow-up had greater utilization of healthcare resources compared with those with no progression during the same time period. Patients with progression (vs without progression) were significantly more likely to have at least one inpatient admission (54.5 vs 18.1%, $p < 0.0001$) and at least one ER visit (61.4 vs 32.3%, $p < 0.0001$). In addition, patients with progression had a significantly ($p < 0.001$) higher mean number of inpatient admissions, ER visits, radiology services and other outpatient services compared with patients without progression (Table 2). Patients without progression (vs with progression) had a larger mean (SD) number of pharmacy prescriptions for antineoplastic treatments PPPM (1.1 [0.2] vs 0.8 [0.3], $p < 0.001$) during the first 12 months of follow-up due to

longer continuation on their index EGFR-TKI. Utilization of office-administered antineoplastic treatments were therefore higher among those with progression (vs without progression) due to line of therapy advancement (i.e., either adding or switching to infused agents in the second line for ∼40% of patients Table 2).

Adjusted mean (SD) total healthcare costs PPPM were significantly higher for patients with (vs without) progression in the first 12 months of follow-up ($19,927 [$5,885] vs $17,527 [$5,737]; $p = 0.002$). The cost difference was more pronounced after excluding antineoplastic treatment costs ($11,480 [SD $4,752] vs $4,996 [SD $1,974]; $p < 0.001$ Figure 5). Unadjusted costs were significantly higher among patients with progression across most services categories (vs without progression) with those progressing in months 0–6 the most costly (Table 3 & Figure 6). Inpatient admissions were the most notable driver of cost differences with mean (SD) costs PPPM $808 ($2872) for nonprogressors, compared with $7508 ($19,080) and $3,882 ($9792) for those who progressed in months 0–6 and 7–12, respectively (Table 3 & Figure 6).

Adjusted monthly predicted cumulative costs for medical services (excluding antineoplastic costs) were significantly higher among patients who progressed early (months 0–12) compared with patients who progressed late (months 13–36). Total costs (medical services + antineoplastic treatment costs) trended higher for early progressors (Figure 7), however, between group differences were attenuated by the higher treatment costs among those with late progression who remained on first-line EGFR TKIs for a more extended period of time.

4. Discussion

This real-world analysis is among the first to examine the economic burden of early disease progression among US patients with EGFRm NSCLC who received an EGFR TKI as first-line treatment for metastatic disease. This study augments prior literature that included a broad cohort of patients with metastatic lung cancer, irrespective of disease histology or genomic mutational status, with more recent data specific to patients with a common EGFR mutation and treated with targeted therapy [2,15,18]. In addition, by linking our population to the NDI to accurately capture patient mortality in the real-world setting this analysis further highlights the importance of PFS beyond what is available from clinical trials. Of the 228 patients with EGFRm mNSCLC, 66.7% (n = 152) experienced disease progression over 36 months, and (n = 101) 44.3% progressed within 12 months of initiating treatment with an EGFR TKI. This is consistent with clinical trials which have shown that first-line treatment with
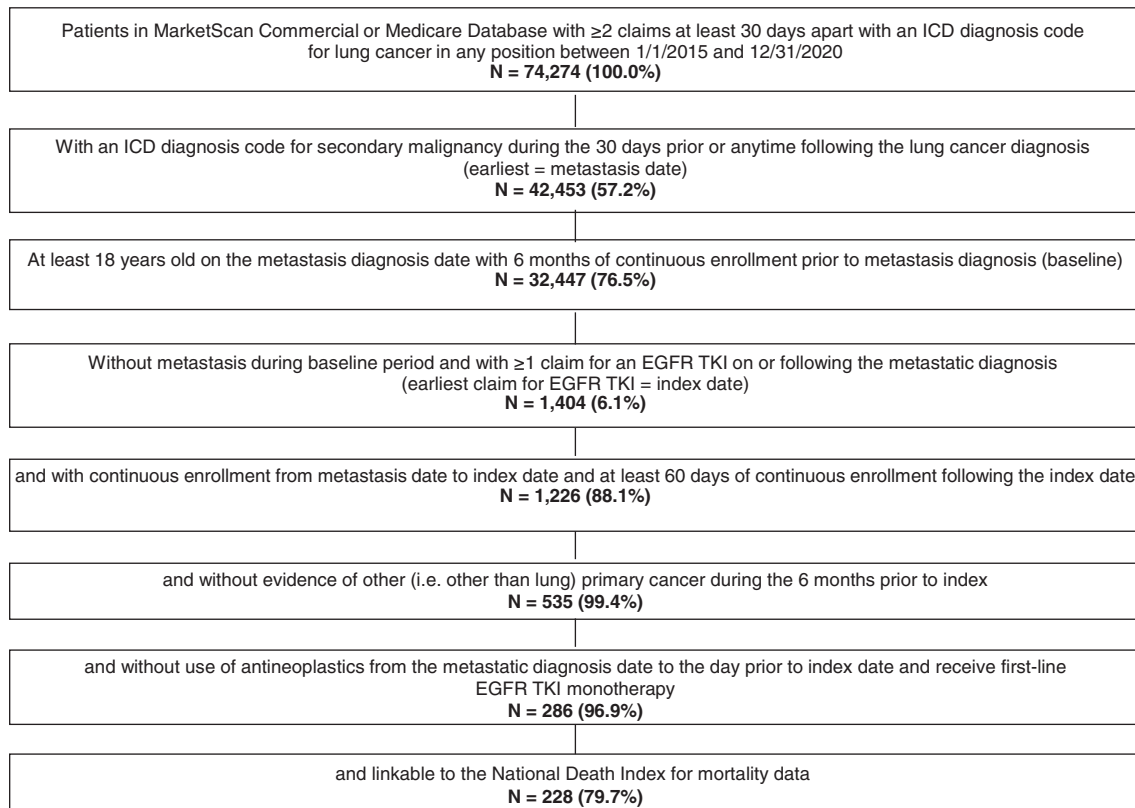
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┌─────────────────────────────────────────────────────────────────────────────┐
│ Patients in MarketScan Commercial or Medicare Database with ≥2 claims at      │
│ least 30 days apart with an ICD diagnosis code for lung cancer in any         │
│ position between 1/1/2015 and 12/31/2020                                      │
│ N = 74,274 (100.0%)                                                           │
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│ With an ICD diagnosis code for secondary malignancy during the 30 days prior  │
│ or anytime following the lung cancer diagnosis                                │
│ (earliest = metastasis date)                                                  │
│ N = 42,453 (57.2%)                                                            │
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│ At least 18 years old on the metastasis diagnosis date with 6 months of       │
│ continuous enrollment prior to metastasis diagnosis (baseline)                │
│ N = 32,447 (76.5%)                                                            │
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│ Without metastasis during baseline period and with ≥1 claim for an EGFR TKI   │
│ on or following the metastatic diagnosis                                      │
│ (earliest claim for EGFR TKI = index date)                                    │
│ N = 1,404 (6.1%)                                                              │
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│ and with continuous enrollment from metastasis date to index date and at      │
│ least 60 days of continuous enrollment following the index date               │
│ N = 1,226 (88.1%)                                                             │
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│ and without evidence of other (i.e. other than lung) primary cancer during    │
│ the 6 months prior to index                                                   │
│ N = 535 (99.4%)                                                               │
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│ and without use of antineoplastics from the metastatic diagnosis date to the  │
│ day prior to index date and receive first-line EGFR TKI monotherapy           │
│ N = 286 (96.9%)                                                               │
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│ and linkable to the National Death Index for mortality data                   │
│ N = 228 (79.7%)                                                               │
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Figure 2. Patient identification.
EGFR: Epidermal growth factor receptor; ICD: International classification of diseases; TKI: Tyrosine kinase inhibitor.
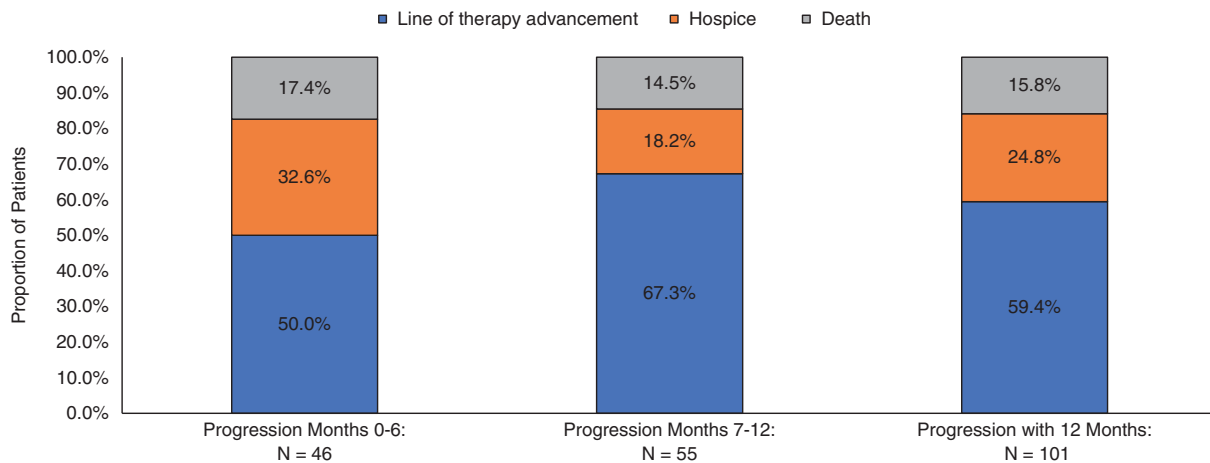

Figure 3. First progression event in first 12 months of follow-up among patients with metastatic non-small-cell lung cancer epidermal growth factor receptor activating mutation following initiation of first-line treatment on an epidermal growth factor receptor tyrosine kinase inhibitor.
EGFRm: Epidermal growth factor receptor activating mutation; mNSCLC: Metastatic non-small-cell lung cancer; TKI: Tyrosine kinase inhibitor.

EGFR-TKIs (osimertinib, erlotinib, afatinib and gefitinib) extend PFS to 10–18 months [7–10].

In the adjusted analysis, our results showed a significant increase in total PPPM costs for patients with progression in the first 12 months after first-line treatment initiation, compared with those with no progression. However, the cost difference was attenuated by the antineoplastic agents prescribed. All patients without progression were treated with EGFR TKIs, whereas upon progression, infused agents were incorporated into treatment regimens. When antineoplastics were excluded from the analysis, costs for medical services were more

Table 1. Characteristics of patients with metastatic non-small cell lung cancer epidermal growth factor receptor activating mutation with and without disease progression in the first 12 months following initiation of first-line of an epidermal growth factor receptor tyrosine kinase inhibitor.

	All patients (n = 228)		No disease progression in the first 12 Months (n = 127)		With disease progression in the first 12 months (n = 101)		p-value[1]
Age: mean, SD	63.0	12.4	61.6	11.6	64.7	13.2	0.062
Female: n, %	151	66.2%	81	63.8%	70	69.3%	0.381
Payer: n, %							
Commercial insurance	140	61.4%	84	66.1%	56	55.4%	0.099
Medicare supplemental insurance	88	38.6%	43	33.9%	45	44.6%	
Insurance plan type: n,%							
Comprehensive/indemnity	38	16.7%	17	13.4%	21	20.8%	0.084
EPO/PPO	123	53.9%	69	54.3%	54	53.5%	
POS/POS with capitation	11	4.8%	4	3.1%	7	6.9%	
HMO	24	10.5%	14	11.0%	10	9.9%	
CDHP/HDHP	31	13.6%	23	18.1%	8	7.9%	
Other/Unknown	1	0.4%	0	0.0%	1	1.0%	
Index year: n, %							
2015–2017	154	67.5%	70	55.1%	84	83.2%	**0.000**
2018–2020	74	32.5%	57	44.9%	17	16.8%	**0.000**
National Cancer Institute Index (NCI): mean, SD	0.4	0.4	0.4	0.4	0.5	0.5	0.090
Duration of follow-up (days): mean, SD	551.0	316.4	563.9	335.0	444.5	279.1	**0.004**
First line TKI (N, %)							
Erlotinib	99	43.4%	41	32.3%	58	57.4%	**0.000**
Osimertinib	77	33.8%	57	44.9%	20	19.8%	**0.000**
Afatinib	49	21.5%	26	20.5%	23	22.8%	0.675
Gefitinib	3	1.3%	3	2.4%	0	0.0%	0.120

Bolded indicates p < 0.05.
CDHP: Consumer-driven health plan; EGFRm: Epidermal growth factor receptor activating mutation; EPO: Exclusive provider organization; HDHP: High deductible health plan; HMO: Health maintenance organization; mNSCLC: Metastatic non-small-cell lung cancer; POS: Point of service; PPO: Preferred provider organization; SD: Standard deviation; TKI: Tyrosine kinase inhibitor.
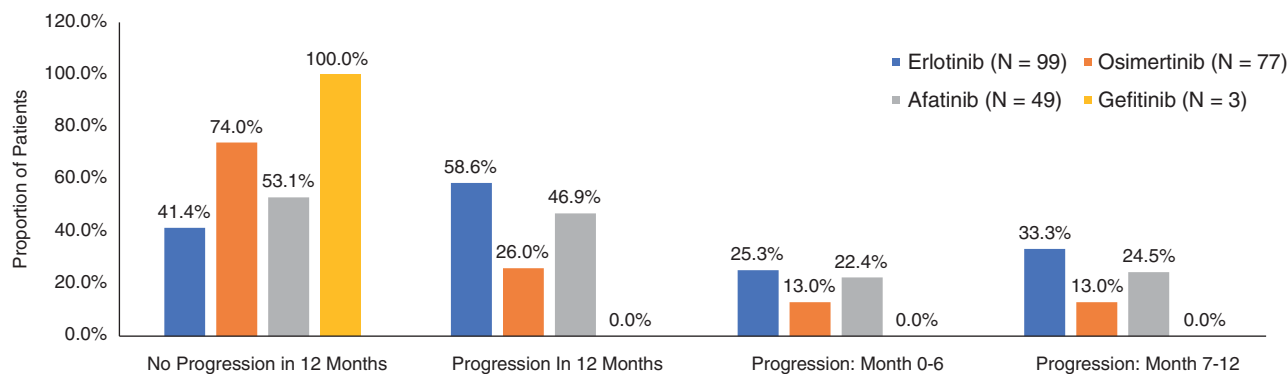
Figure 4. First-line epidermal growth factor receptor tyrosine kinase inhibitor by progression status in the first 12 months.

than two-times higher for progressors versus nonprogressors within 12 months. Inpatient stays accounted for 4.7% of total PPPM costs for patients with no progression, and 27.4/32.8% for those with progression in the first 12/6 months of follow-up. These data are consistent with prior studies among patients with advanced NSCLC that have shown that hospitalization and anticancer treatment together account for the majority of total mean monthly costs [19]. The reduced number of hospitalizations, shorter length of inpatient stays, and lower hospitalization costs during first-line TKI therapy (e.g., prior to progression vs following progression) suggest treatments

that delay progression may offer improved quality of care for lower medical costs for patients with EGFRm NSCLC.

Patients with progression in months 0–6 after first-line treatment initiation had higher PPPM medical costs than those who progressed in months 7–12, primarily driven by inpatient stays. It is possible that these individuals had more advanced disease upon metastatic diagnosis or a poor response to first-line EGFR TKIs compared with those who progressed later [20]. A poor prognosis is suggested by our data. Among progressors in the first 6 months, 50% of the events were attributable to hospice care or death

Table 2. Healthcare resource utilization measured per patient per month among patients with metastatic non-small-cell lung cancer epidermal growth factor receptor activating mutation with and without disease progression within 12 months after first-line initiation on an epidermal growth factor receptor activating tyrosine kinase inhibitor.

	No disease progression in the first 12 months n = 127	With disease progression in the first 12 months n = 101	p-value (w/progression vs no progression)	Disease progression in months 0–6 n = 46	p-value (w/progression in months 0–6 vs no progression)	Disease progression in months 7–12 n = 55	p-value (w/progression in months 7–12 vs no progression)
Inpatient							
Patients with ≥1 admission: n, %	23, 18.1%	55, 54.5%	**0.000**	24, 52.2%	**0.000**	31, 56.4%	**0.000**
Number of admissions, PPPM: mean, SD	0.03, 0.08	0.11, 0.40	**0.000**	0.13, 0.53	**0.000**	0.09, 0.30	**0.000**
Length of stay (in days) per admission: mean, SD	0.08, 0.21	0.40, 0.68	**0.000**	0.53, 0.87	**0.000**	0.30, 0.45	**0.000**
Outpatient							
Emergency room visits							
Patients with ≥1 emergency room visit: n, %	41, 32.3%	62, 61.4%	**0.000**	25, 54.3%	**0.008**	37, 67.3%	**0.000**
Number of emergency room visits, PPPM: mean, SD	0.04, 0.08	0.13, 0.17	**0.000**	0.16, 0.22	**0.000**	0.11, 0.12	**0.000**
Office-administered antineoplastics							
Patients with ≥1 administration: n, %	0, 0.0%	31, 30.7%	**0.000**	12, 26.1%	**0.000**	19, 34.5%	**0.000**
Number of administrations, PPPM: mean, SD	0.00, 0.00	0.18, 0.37	**0.000**	0.19, 0.44	**0.000**	0.17, 0.31	**0.000**
Outpatient office visits							
Patients with ≥1 office visit: n, %	126, 99.2%	98, 97.0%	0.324	43, 93.5%	0.058	55, 100.0%	1.000
Number of office visits, PPPM: mean, SD	1.87, 1.08	1.90, 1.08	0.844	1.80, 1.13	0.712	1.98, 1.04	0.523
Outpatient radiology							
Patients with ≥1 radiology service: n, %	125, 98.4%	98, 97.0%	0.657	44, 95.7%	0.288	54, 98.2%	1.000
Number of radiology services, PPPM: mean, SD	2.01, 2.57	2.90, 3.09	**0.003**	3.61, 3.69	**0.002**	2.66, 1.96	0.098
Outpatient laboratory services							
Patients with ≥1 laboratory service: n, %	123, 96.9%	94, 93.1%	0.222	40, 87.0%	**0.023**	54, 98.2%	1.000
Number of laboratory services, PPPM: mean, SD	3.74, 3.32	3.66, 2.91	0.860	2.88, 2.53	0.111	4.32, 3.06	0.265
Other outpatient services†							
Patients with ≥1 other outpatient service: n, %	125, 98.4%	101, 100.0%	0.504	46, 100.0%	1.000	55, 100.0%	1.000
Number of other outpatient services, PPPM: mean, SD	2.30, 1.72	3.66, 3.54	**0.000**	3.65, 3.57	**0.001**	3.67, 3.55	**0.001**
Outpatient pharmacy							
Patients with a ≥1 prescription (any): n, %	127, 100.0%	101, 100.0%	1.000	46, 100.0%	1.000	55, 100.0%	1.000
Number of prescriptions, PPPM: mean, SD	4.15, 2.31	3.93, 1.91	0.448	4.07, 1.93	0.827	3.82, 1.90	0.355
Patients with ≥1 prescription (antineoplastics): n, %	127, 100.0%	101, 100.0%	1.000	46, 100.0%	1.000	55, 100.0%	1.000
Number of prescriptions, PPPM: mean, SD	1.07, 0.24	0.75, 0.33	**0.000**	0.71, 0.33	**0.000**	0.79, 0.33	**0.000**
Hospice Care							
Patients with any hospice care: n, %		38, 37.6%	n/a	21, 45.7%	n/a	17, 30.9%	n/a
Patients with inpatient hospice care: n, %		16, 15.8%	n/a	10, 21.7%	n/a	6, 10.9%	n/a
Patients with outpatient hospice care: n, %		29, 28.7%	n/a	16, 34.8%	n/a	13, 23.6%	n/a

†Inclusive of all other outpatient services not reported out individually.
EGFRm: Epidermal growth factor receptor activating mutation; mNSCLC: Metastatic non-small-cell lung cancer; PPPM: Per patient per month; SD: Standard deviation; TKI: Tyrosine kinase inhibitor.
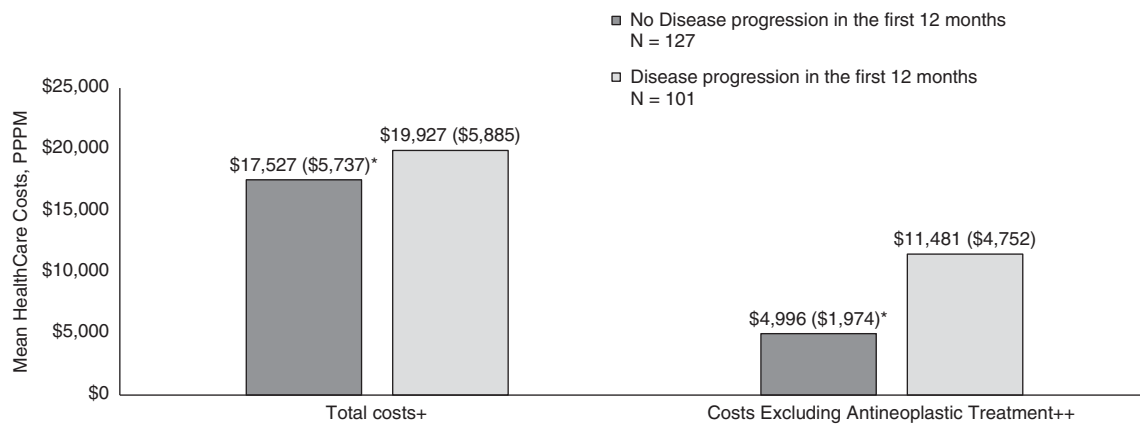Bolded indicates $p < 0.05$.
n/a: Not applicable.

Figure 5. Adjusted total healthcare costs measured per patient per month among patients with metastatic non-small-cell lung cancer epidermal growth factor receptor activating mutation with and without disease progression within 12 months after first-line initiation on an epidermal growth factor receptor activating tyrosine kinase inhibitor.
*Comparison $p \leq 0.05$ versus no disease progression.
+ Total costs include medical costs (inpatient and outpatient services) as well as pharmacy costs.
++ Both medical (for office administrated treatments) and pharmacy (for treatments filled at a pharmacy) costs for antineoplastic therapy are removed.
EGFRm: Epidermal growth factor receptor activating mutation; mNSCLC: Metastatic non-small-cell lung cancer; PPPM: Per patient per month; TKI: Tyrosine kinase inhibitor.

Table 3. Unadjusted healthcare costs measured per patient per month among patients with metastatic non-small-cell lung cancer epidermal growth factor receptor activating mutation with and without disease progression within 12 months after first-line initiation on an epidermal growth factor receptor tyrosine kinase inhibitor.

PPPM healthcare costs; Mean (SD)	No disease progression in the first 12 months (n = 127)	Disease progression in the first 12 months (n = 101)	Disease progression in months 0–6 (n = 46)	Disease progression in months 7–12 (n = 55)
Inpatient	$808 ($2872)	$5533 ($14,795)[§]	$7508 ($19,080)[§]	$3882 ($9792)[§]
Outpatient medical[†]	$3923 ($4299)	$6633 ($7004)[§]	$7374 ($6518)[§]	$6,013 ($7387)[§]
Emergency room	$56 ($160)	$362 ($1146)[§]	$485 ($1548)[§]	$259 ($642)[§]
Office administered antineoplastics	$2 (22)	$1106 ($2482)[§]	$1205 ($2847)[§]	$1024 ($2152)[§]
Infusion costs (i.e., administration costs for antineoplastics)[†]	$0.3 ($3)	$60 ($153)[§]	$75 ($193)[§]	$48 ($108)[§]
Office visits	$310 ($253)	$265 ($177)	$254 ($196)	$273 ($161)
Radiology services	$1689 ($2658)	$2498 ($5240)	$2838 ($3966)[§]	$2213 ($6128)
Laboratory services	$238 ($378)	$324 ($564)	$383 ($736)	$274 ($365)
Other outpatient services[‡]	$1630 ($1936)	$3185 ($3488)[§]	$3414 ($3796)[§]	$2993 ($3231)[§]
Total medical (inpatient + outpatient services + outpatient treatment)	$4731 ($5333)	$12,167 ($16,944)[§]	$14,883 ($20,152)[§]	$9895 ($13,480)[§]
Outpatient pharmacy	$12,639 ($5077)	$8017 ($4593)[§]	$7990 ($5233)[§]	$8040 ($4030)[§]
Antineoplastic pharmacy prescription costs	$12,319 ($5,080)	$7652 ($4522)[§]	$7718 ($5214)[§]	$7597 ($3899)[§]
Other pharmacy prescription costs	$319 ($433)	$365 ($778)	$271 ($373)	$443 ($996)
Total (medical + pharmacy)	$17,370 ($8285)	$20,184 ($18,068)	$22,872 ($21,848)[§]	$17,936 ($13,982)
Total (excluding all antineoplastic treatment costs both medical and pharmacy)	$5049 ($5401)	$11,425 ($16,810)[§]	$13,949 ($20,004)[§]	$9314 ($13,410)[§]

[†]Procedure codes for antineoplastic administration.
[‡]Inclusive of all other outpatient services not reported out individually.
[§]Comparison $p \leq 0.05$ versus no disease progression.
EGFRm: Epidermal growth factor receptor activating mutation; mNSCLC: Metastatic non-small-cell lung cancer; PPPM: Per patient per month; SD: Standard deviation; TKI: Tyrosine kinase inhibitor.

compared with only 33% for progressors in months 7–12. In the analysis of early versus late progression over 36 months, results remained consistent. Patients with early progression had significantly higher cumulative predicted medical costs each month compared with those with late progression. The inverse was true for antineoplastics with late progressors having higher drug costs attributable to a longer duration of treatment with EGFR TKIs.

These data highlight the need for better treatment options to delay progression. Reyes et al. conducted a similar analysis reporting the costs of disease progression among patients with metastatic breast, colorectal and lung cancer using data from 2007–2014. Metastatic
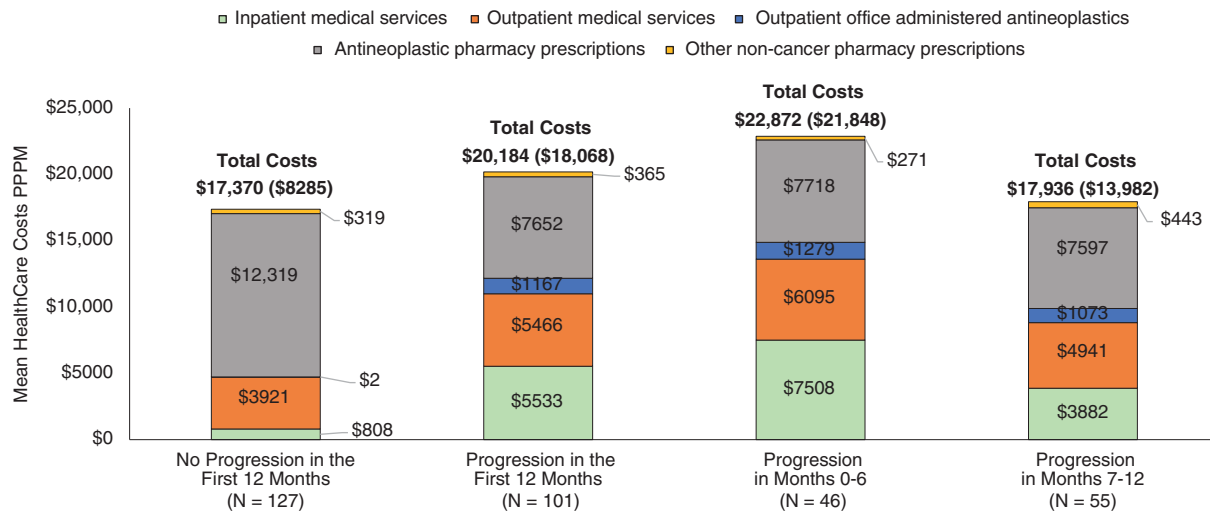
Figure 6. Unadjusted healthcare costs by service category measured per patient per month among metastatic non-small-cell lung cancer epidermal growth factor receptor activating mutation patients with and without disease progression within 12 months after first-line initiation on an epidermal growth factor receptor tyrosine kinase inhibitor.
EGFRm: Epidermal growth factor receptor activating mutation; mNSCLC: Metastatic non-small-cell lung cancer; PPPM: Per patient per month; TKI: Tyrosine kinase inhibitor.

lung cancer was shown to have the highest rate of progression within 12 months (compared with breast and colorectal). The current analysis identified a specific cohort of EGFRm mNSCLC patients with progression in months 0–6, 7–12 (early progressors) compared with those who progressed later (months 13–36) and found that those who progressed in the earliest months had the highest costs providing further support suggesting that delaying disease advancement (through availability of more effective treatment options) may reduce medical costs. These findings are relevant both for payers (as lower medical costs incurred by delaying disease advancement may offset treatment costs) and for clinicians of whom many of their patients are covered under Medicare plans. The Enhancing Oncology Model announced in June 2022 (from the Center of Medicare and Medicaid Innovation) provides financial incentives for employing cost-effective practices. Understanding costs overtime (and the impact of early progression) may help payers anticipate their annual budgets and help providers participating in value-based programs manage the total cost of care for their patients [21]. New treatment options are needed for patients with EGFRm mNSCLC that have a longer duration of disease control both in the first line setting and also in later line settings where options are further limited.

This study is subject to several limitations. While administrative claims data provide detailed cost information for a diverse group of real-world patients, not all clinical information is recorded. Biomarker results and lung cancer histology were not available,

therefore, treatment with afatinib, erlotinib, gefitinib or osimertinib was used as a proxy to identify EGFRm NSCLC. Although afatinib, erlotinib, gefitinib and osimertinib are most often prescribed to address common EGFR mutations, using these targeted agents as a proxy for the identification of patients with an exon 19 deletion or L858R mutation may result in some misclassification. Metastatic disease was determined based on claims evidence of a secondary neoplasm and may be subject to coding inaccuracies. Physician documented disease progression was unavailable, therefore, an algorithm comprised of line of therapy advancement, evidence of hospice care coded on medical claims, and death was used to identify disease progression. Of note, some patients who advanced to a subsequent line of therapy may have done so for reasons other than disease progression and therefore may have been misclassified. In addition, the MarketScan commercial and Medicare databases are convenience samples of employees, retirees and dependents with US commercial and Medicare health insurance coverage. Future analyses in alternative datasets and with a larger sample size are needed to augment study findings and improve generalizability to patients with other insurance types (e.g., Medicaid) or who lack healthcare coverage needs to be confirmed in future studies.

5. Conclusion

Given that the cost of oncology care has been increasing dramatically over the past decade and with increases
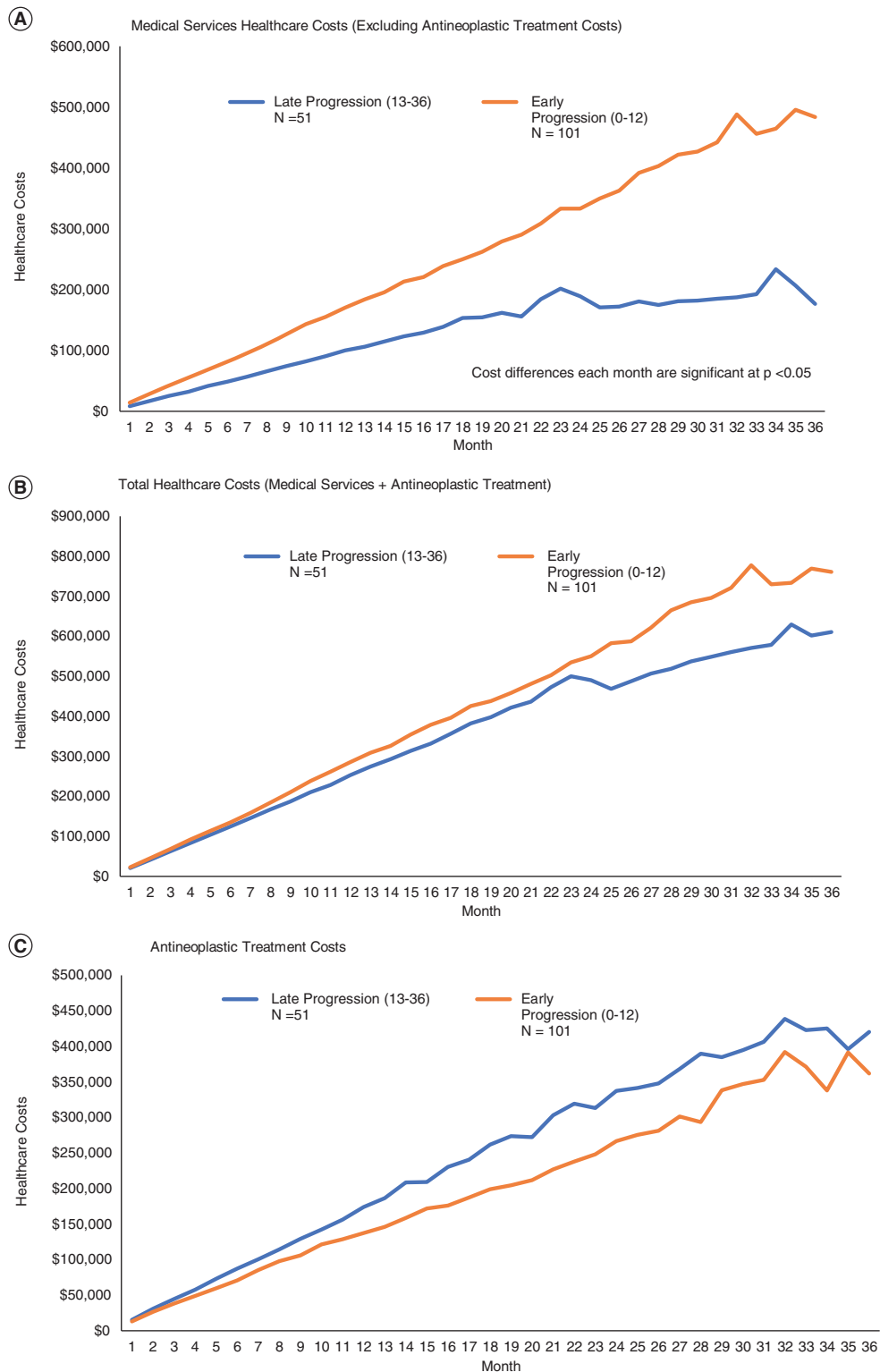
Figure 7. Adjusted* cumulative weighted predicted costs for among patients with metastatic non-small-cell lung cancer epidermal growth factor receptor activating mutation that progress early (months 0–12) versus late (months 13–36) after initiation on a first-line epidermal growth factor receptor tyrosine kinase inhibitor. **(A)** Medical services healthcare costs (excluding antineoplastic treatment costs). **(B)** Total healthcare costs (medical services + antineoplastic treatment). **(C)** Antineoplastic treatment costs.
*Models adjusted for age, gender, region, health plan type, year of first line treatment initiation, comorbidity index score and first line EGFR TKI.
**Statistical significance reported for each month has some variation, *p*-values are less than 0.05 for all months in model a.
EGFRm: Epidermal growth factor receptor activating mutation; mNSCLC: Metastatic non-small-cell lung cancer; TKI: Tyrosine kinase inhibitor.

expected to continue [13] the need for data quantifying how costs for both medical services and treatments are impacted by disease progression is paramount. The results from this analysis suggest that patients with EGFRm mNSCLC with disease progression in the first 12 months following initiation of an EGFR TKI incurred significantly higher total costs despite having lower treatment costs compared with patients without disease progression in the first 12 months. Cost burden was highest among those with progression in the first 6 months, driven primarily by hospitalizations substantiating the need for improved treatment options to delay disease advancement. These data may help inform oncology providers aiming to administer high quality cancer care in a cost-efficient way.

Article highlights

- Patients with non-small-cell lung cancer face a high burden of healthcare costs, especially when the disease progresses.
- This was a retrospective study using administrative claims data of 228 adult patients with epidermal growth factor receptor mutated (EGFRm) metastatic non-small-cell lung cancer (mNSCLC) that initiated a first-line EGFR tyrosine kinase inhibitor (TKI) between 2015 and 2020.
- Healthcare costs were captured during the first 12 months after treatment initiation in patients with and without disease progression, and cumulative costs were predicted over 36 months for patients with early (post initiation months 0–6) versus late (post initiation months 7–12) disease progression.
- There were 152 (66.7%) patients whose disease progressed at any time during the 12 months after treatment initiation; 101 (66.4%) patients had early progression and 51 (34.2%) had late progression.
- Patients with any disease progression had greater healthcare resource utilization compared with patients whose disease did not progress during follow-up.
- Adjusted mean total healthcare costs were statistically significantly higher for patients with any progression compared with those without progression, mainly driven by inpatient costs.
- Adjusted monthly predicted cumulative costs were significantly higher among patients who progressed early compared with those that progressed late.
- Study limitations include lack of biomarker and histology data from claims data, misclassification of metastatic disease status and specific EGFR mutations based on coding errors and limited generalizability.
- This studies provides real-world costs of patients with EGFRm mNSCLC that initiate a TKI whose disease progresses in a 12-month time period; the cost burden was highest among patients with disease progression in the first 6 months after treatment initiation.
- This study highlights the importance of delaying EGFRm mNSCLC disease progression in a timely manner.

Author contributions

N Princic, E Marrett, WJ Kwong, D McMorrow and H Schwartz contributed to conception, design, and planning of the study, analysis of the data and interpretation of the results and drafting of the manuscript. J Subramanian contributed to interpretation of the results, as well as critically reviewing the manuscript for important intellectual content.

Financial disclosure

Competing interests disclosure

Writing disclosure

Ethical conduct of research

Data availability statement

The data that support the findings of this study are available from Merative. Restrictions apply to the availability of these data, which were used under license for this study.

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