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ORIGINAL ARTICLE

Treatment adherence, healthcare resource utilization, and costs in patients with lung neuroendocrine tumors (lung NETs) in the USA

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ABSTRACT

Objective: To assess first-line treatment adherence, healthcare resource utilization, and costs in lung NET patients initiating pharmacologic treatments.

Methods: In two US claims databases, patients aged ≥18 years with ≥1 inpatient or ≥2 outpatient lung NET claims within 12 months were identified. The first claim for pharmacologic treatments (e.g. somatostatin analogs [SSAs], cytotoxic chemotherapy [CC], targeted therapy [TT]) following diagnosis, between July 1, 2009–December 31, 2014, was defined as the index date. A 6-month pre-index period without any NET treatment, and ≥1-year post-index enrollment were required. Proportion of days covered (PDC) was calculated during follow-up. Descriptive statistics, including means, standard deviations, and frequencies/percentages for continuous and categorical data, respectively, were reported.

Results: Of 354 patients with 1-year of follow-up, 252 initiated CC, 89 SSA, 3 TT, and 10 various combinations. Due to sample sizes, the remaining results focus only on CC and SSAs. Mean PDC (SD) was 0.320 (0.176) for CC and 0.673 (0.322) for SSAs; CC users had a mean (SD) of 33.3 (23.8) office visits and 0.79 (1.39) hospitalizations; SSA users had 23.1 (12.4) visits and 0.48 (1.07) hospitalizations. Mean total (SD) annual cost for CC users was $124,383 (135,836) and $98,713 (81,495) for SSA users. Among 163 patients with 2 years of follow-up, the annual mean cost in the second-year was $43,026 lower and $8110 higher than the first-year for CC and SSAs, respectively.

Conclusions: The majority of patients with lung NETs initiated CC; only about one quarter initiated SSA in the first-line. This descriptive study updates the utilization and costs of pharmacologically-treated lung NETs.

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Lung neuroendocrine tumors; Treatment adherence; Insurance claims; Resource utilization; Costs

Introduction

Neuroendocrine tumors (NETs) are rare and often slow growing malignancies. They may arise from neuroendocrine cells anywhere in the body[1,2], although approximately one quarter of NET occur in the lungs[3]. A sub-set of NETs secrete peptides and neuroamines that cause distinct syndromes (e.g. carcinoid syndrome), in which case they are referred to as "functional" tumors. For largely unknown reasons, the incidence of NET in the US has been increasing, from 10.9 cases per million person-years (PMPY) in 1973 to 69.8 PMPY in 2012. Lung NET incidence rose from 3.0 to 16.0 cases PMPY during the same time frame[4] and was reported as 16.2 PMPY in 2014 using commercial claims[5].

NET treatments are individualized based on tumor size, location, and pathology, as well as whether the tumor is functional, type and extent of symptoms, and speed of progression. The National Comprehensive Cancer Network (NCCN) NET guidelines generally recommend somatostatin analogs (SSA) as first-line treatment for unresectable and/or metastatic disease[3,6,7]. The NCCN small cell lung cancer (SCLC) guidelines in place during the time of this study (before 2017) recommended targeted therapy (TT) or cytotoxic chemotherapy (CC) for most patients with lung NET, reserving SSA for patients with positive octreotide scans or carcinoid syndrome[6,8]. In a recent retrospective analysis, it appeared that more than three-quarters of pharmacologically treated patients began treatment with cytotoxic chemotherapy (e.g. 5-FU, capecitabine, temozolomide)[9]. The next most common initial treatment—just over 18% of patients—was with a variety of SSAs. Other treatments included targeted therapies such as everolimus and sunitinib[9].

A 2013 comprehensive systematic review of multiple databases found quite limited information on resource use, cost of illness, and economic outcomes in general for NETs[10]. To date, there are no data available on treatment adherence, resource utilization, and costs among patients with lung NET. This study, for the first time, uniquely aimed to assess real-world first-line treatment adherence, healthcare resource utilization, and costs in patients with lung NETs who initiated pharmacologic treatments.

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Materials and methods

We conducted a longitudinal, retrospective cohort analysis of newly pharmacologically treated lung NET patients using two large US commercial claims databases—the Truven Health Analytics MarketScan database and the IMS PharMetrics database, both using dates from January 1, 2009, to December 31, 2014. Both databases are Health Insurance Portability and Accountability Act compliant administrative claims databases that contain de-identified adjudicated medical claims (e.g. inpatient and outpatient services) and pharmacy claims (e.g. outpatient prescriptions) submitted for payment by providers, healthcare facilities, and pharmacies. For both data sources, claims include information on each physician visit, medical procedure, hospitalization, drug dispensed, date of service, number of days of medication supplied, test performed, and complete payment information. Each medical claim has a principal diagnosis and secondary diagnoses codes associated with it. Available patient demographic information includes age, gender, and geographic region. Dates of enrollment and disenrollment are also recorded. As the data were fully de-identified, this study was considered exempt from approval by the Institutional Review Board.

Patients $\geq$18 years old were identified from each dataset if they had at least one inpatient or at least two outpatient claims within any 12 months with an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code for lung NET (209.21, 209.61) between July 1, 2009 and December 31, 2014. Due to limited data availability, we excluded patients $\geq$65 years from the analysis. The date of the first lung NET pharmacologic treatment claim on or after the appearance of the lung NET diagnosis code was considered to be the index date. Patients were required to have continuous enrollment for at least 6 months before (baseline) and at least 1 year after the index date. To ensure new treatment, patients with any evidence of pharmacologic treatment for NET during this baseline period were excluded. In order to not include the same patient twice, we searched for any patients with the same age, gender, region, and date of lung NET diagnosis who could be found in both databases, but we found none. Patients were followed for at least 1 year until the end of enrollment.

Patient demographic characteristics (age, gender, US census region) were derived from the enrollment files. Outcomes were reported organized by first observed pharmacologic therapy: SSA, TT, CC (whether given alone or in combination), interferon (IFN), and combinations of these groups. SSA included octreotide and lanreotide, TT included everolimus and sunitinib, and CC included temozolomide, streptozotocin, doxorubicin, liposomal doxorubicin, fluorouracil, capecitabine, dacarbazine, oxaliplatin, and thalidomide. Pharmacologic therapy was identified in claims using both the Healthcare Common Procedure Coding System (HCPCS) and National Drug Codes (NDC). First-line treatments were defined as the pharmacologic treatment regimen observed on, or within 3 months of, the index date. This 3-month window was used to identify pharmacologic therapy intended as first-line but not administered precisely on the index date. This would include, for example, combination chemotherapy where the second agent is given after some delay.

Two adherence measures were calculated: medication possession ratio (MPR) and proportion of days covered (PDC). MPR was calculated as total days of supply for fills within the refill interval divided by days in the refill interval and capped at 100%. Patients with at least two fills of first-line therapy were included. The refill interval was defined as the period between the first fill and the last fill plus the days of supply of the last fill. PDC was calculated as the number of days with first-line therapy available ("covered") divided by the number of days in the review period. PDC was calculated for the 1 year following treatment initiation date, and, thus, the number of days in the review period was 365.

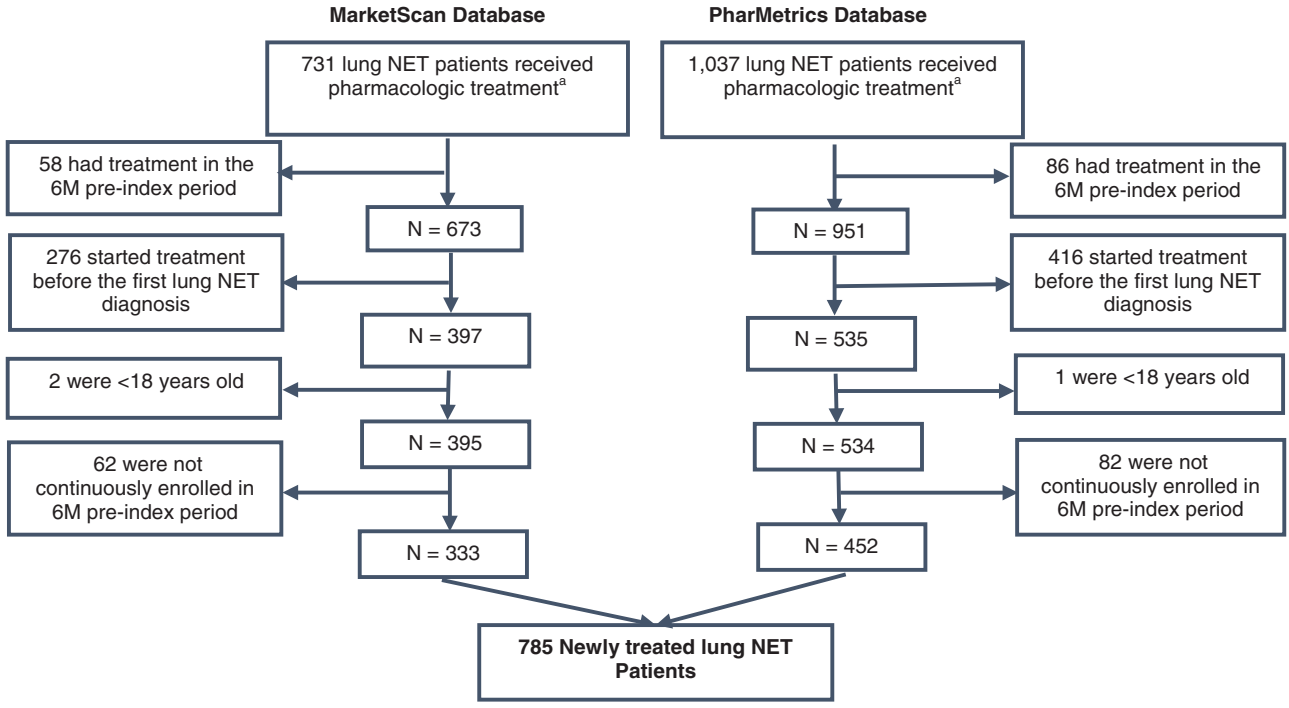
All-cause healthcare utilization included inpatient hospitalizations, emergency department (ED) visits, non-ED outpatient service visits, and any pharmacy utilization. All-cause healthcare costs were calculated by adding up all medical costs, which includes inpatient hospitalization costs, ED service costs, and non-ED outpatient service costs, and pharmacy costs. Costs were for insurance-covered healthcare costs from fully adjudicated and paid claims, and included both patient and plan portions of each claim for all medical services utilized during the study period. Services provided "out-of-network" or not covered by insurance were not included. In addition, we identified cost related to cancer based on claims with a primary ICD-9-CM diagnosis code of 140.xx–239.xx and reported both cancer-related and non-cancer related costs.

Descriptive statistics, including means, standard deviations, and relative frequencies and percentages for continuous and categorical data, were reported. All costs were adjusted to 2014 dollars (the last available year of study data) using the medical care component of the Consumer Price Index. All data transformations and statistical analyses were performed using SAS© version 9.4 (SAS Institute, Cary, NC).

Results

There were 731 and 1037 patients meeting the definition of lung NET who also had a claim for first-line pharmacologic treatment between July 1, 2009 and December 31, 2014 in the MarketScan and PharMetrics databases, respectively. After excluding patients who had treatment during a 6-month pre-index period (and therefore were considered to be continuing, rather than initiating, treatment); received treatment before receiving a diagnosis of lung NET; were $<$18 years old; or were not continuously enrolled in the 6-month pre-index period, there remained 785 newly-treated lung NET patients who were included in the study (Figure 1). Among these, there were 354 patients with at least 1 year, and 168 with at least 2 years of follow-up since treatment initiation (Table 1).

Among the 354 patients with 1 year of follow-up, 89 initiated SSA, 252 CC, three targeted therapies, two IFN, and 10 various combinations (Table 1). Demographic characteristics are shown in Table 2. With regard to adherence, the mean



[a]Somatostatin analogues (SSAs), targeted therapy, cytotoxic chemotherapy, or interferon

Figure 1. Patient identification. There were 731 and 1,037 lung NET patients who also had a claim for pharmacologic treatment between July 1, 2009 and December 31, 2014 in the MarketScan and PharMetrics databases, respectively. After excluding patients who had treatment during a 6-month pre-index period (and therefore were considered to be continuing, rather than initiating, treatment); received treatment before receiving a diagnosis of lung NET; were <18 years old; or were not continuously enrolled in the 6-month pre-index period, there remained 785 newly-treated lung NET patients who were included in the study.

Table 1. First-line treatment in patients with 1 or 2 years post-index enrollment.

	1Y + post-index enrollment	2Y + post-index enrollment
No. of patients	354	168
First line treatment, *n* (%)		
Somatostatin analogs (SSA)	89 (25.1)	49 (29.2)
Cytotoxic Chemo (CC)	252 (71.2)	114 (67.9)
Targeted Therapy (TT)	3 (0.8)	1(0.6)
SSA + CC	5 (1.4)	4 (2.4)
SSA + TT	3 (0.8)	0 (0)
TT + CC	1 (0.3)	0 (0)
SSA + IF	1 (0.3)	0 (0)
Duration of first line treatment during follow-up, days, mean (SD) [median]	298 (313.8) [142]	366 (400.3) [146]

(SD) MPR was 0.823 (0.216) for SSA, 0.846 (0.247) for CC, and 0.801 (0.263) for TT. The mean (SD) PDC was 0.673 (0.322) for SSA, 0.320 (0.176) for CC, and 0.404 (0.164) for TT. With regard to resource use, SSA users had a mean (SD) of 23.1 (12.4) outpatient visits and 0.48 (1.07) hospitalizations. CC users had 33.3 (23.8) and 0.79 (1.39) outpatient visits and hospitalizations, respectively (Table 3).

Total annual cost (SD) for these 89 SSA users during the 1st year was $98,713 (81,495), comprising $46,514 (47,480) in cancer-related and $42,025 (55,698) in non-cancer-related costs. For the 252 CC users, total annual cost was $124,383 (135,836), cancer-related cost was $53,400 (51,101), and non-cancer-related cost was $62,562 (105,513) (Table 4).

Among the 168 patients with 2 years of follow-up, 49 initiated treatment with SSA, 114 CC, one TT, and four combinations.

Mean (SD) number of outpatient visits in years 1 and 2, respectively, were 22.6 (11.0) and 21.7 (13.2) for SSA, and 31.3 (22.3) and 18.6 (15.7) for CC. Mean number of hospitalizations in years 1 and 2, respectively, were 0.55 (1.35) and 0.78 (1.23) for SSA, and 0.54 (0.94) and 0.34 (0.93) for CC. Total annual costs in years 1 and 2, respectively, were $97,301 (72,952) and $105,411 (119,251) for SSA, and $95,696 (89,824) and $52,670 (67,635) for CC (Table 5).

Discussion

This study used two very large, nationally representative claims databases, which together represent up to 100 million covered lives, to study medication adherence, utilization, and cost in pharmacologically treated patients with lung NETs. Several findings were of particular interest. First, with regard to treatment patterns, more than 70% of patients initiated treatment with CC, ~25% SSA, and under 1% TT. The mean PDC for SSA was 0.673, and 0.320 for CC. Second, regardless of initial pharmacologic therapy, utilization and cost are high for this group of patients. First-line therapy is associated with costs over $100,000 in the first-year post-index. Patients had a mean of 30 office visits per year, and nearly 40% had an ED visit or hospitalization.

In this study, we observed that more than 70% of patients initiated CC and 25% initiated SSA. Through 2016, NCCN described treatment of lung NET in two separate guidelines: NET and SCLC; beginning in 2017, the algorithm has only been presented in the NET guidelines. For typical lung NET, the guidelines mention chemotherapy as a Category 3 recommendation (major NCCN disagreement that the intervention is appropriate) only if other treatment options are not

Table 2. Demographic characteristics in patients with 1-year post-index continuous enrollment.

	Somatostatin analogs (SSA)	Cytotoxic Chemo (CC)	Targeted Therapy (TT)	SSA + CC	SSA + TT	TT + CC	SSA + IF	All newly-treated patients
n (%)	89 (25.1)	252 (71.2)	3 (0.8)	5 (1.4)	3 (0.8)	1 (0.3)	1 (0.3)	354 (100.0)
Age, years, mean (SD)	56.5 (10.0)	57.8 (8.9)	64.3 (10.1)	54.6 (5.9)	58.3 (2.5)	62.0 (0)	49.0 (0)	57.5 (9.1)
25–34, *n* (%)	1 (1.1)	4 (1.6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	5 (1.4)
35–44, *n* (%)	9 (10.1)	18 (7.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	27 (7.6)
45–54, *n* (%)	27 (30.3)	52 (20.6)	0 (0)	3 (60.0)	0 (0)	0 (0)	1 (100.0)	83 (23.4)
55–64, *n* (%)	40 (44.9)	137 (54.4)	2 (66.7)	2 (40.0)	3 (100.0)	1 (100.0)	0 (0)	185 (52.3)
65+, *n* (%)	12 (13.5)	41 (16.3)	1 (33.3)	0 (0)	0 (0)	0 (0)	0 (0)	54 (15.3)
Female	56 (62.9)	141 (56.0)	0 (0)	3 (60.0)	2 (66.7)	1 (100.0)	1 (100.0)	204 (57.6)
Region								
Midwest	23 (25.8)	50 (19.8)	1 (33.3)	1 (20.0)	0 (0)	0 (0)	0 (0)	75 (21.2)
Northeast	20 (22.5)	75 (29.8)	1 (33.3)	0 (0)	1 (33.3)	0 (0)	0 (0)	97 (27.4)
South	32 (36.0)	106 (42.1)	0 (0)	3 (60.0)	2 (66.7)	1 (100.0)	0 (0)	144 (40.7)
West	14 (15.7)	21 (8.3)	1 (33.3)	1 (20.0)	0 (0)	0 (0)	1 (100.0)	38 (10.7)
Medication possession ratio among patients with 2+ fills[a,b], *n* (mean) [SD]	84 (0.823) [0.216]	238 (0.846) [0.247]	3 (0.801) [0.263]	n/a	n/a	n/a	n/a	n/a
Proportion of days covered in first year since index date[a], mean (SD)	0.673 (0.322)	0.320 (0.176)	0.404 (0.164)	n/a	n/a	n/a	n/a	n/a

[a]For first-line mono-therapy only.
[b]Number of patients with two or more fills of first line monotherapy.

Table 3. All-cause healthcare resource utilization in patients with 1-year post-index continuous enrollment.

	Somatostatin analogs (SSA)	Cytotoxic chemo (CC)	All
n (%)	89 (26.1)	252 (73.9)	341 (100.0)
No. of office visits	23.1 (12.4)	33.3 (23.8)	30.6 (21.8)
No. of ED visits	0.84 (2.06)	0.71 (1.28)	0.74 (1.52)
0	57 (64.0)	157 (62.3)	214 (62.8)
1	20 (22.5)	55 (21.8)	75 (22.0)
2	4 (4.5)	21 (8.3)	25 (7.3)
3+	8 (9.0)	19 (7.5)	27 (7.9)
No. of inpatient hospitalizations	0.48 (1.07)	0.79 (1.39)	0.71 (1.32)
0	62 (69.7)	148 (58.7)	210 (61.6)
1	19 (21.3)	60 (23.8)	79 (23.2)
2	5 (5.6)	22 (8.7)	27 (7.9)
3+	3 (3.4)	22 (8.7)	25 (7.3)
No. of patients with ≥1 hospitalization, *n* (%)	27 (30.3)	104 (41.2)	131 (38.4)
Days of stay among patients with hospitalizations, mean (SD)	7.6 (13.7)	10.1 (13.9)	9.6 (13.8)

Table 4. All-cause healthcare costs in patients with 1-year post-index continuous enrollment.

	Somatostatin analogs (SSA)	Cytotoxic Chemo (CC)	All
n (%)	89 (26.1)	252 (73.9)	341 (100.0)
Total costs	$98,713 (81,495)	$124,383 (135,836)	$117,683 (124,370)
Total outpatient pharmacy costs	$10,174 (15,324)	$8422 (14,825)	$8879 (14,954)
Total medical (non-outpatient pharmacy) costs	$88,539 (79,912)	$115,962 (132,416)	$108,804 (121,418)
Total inpatient hospitalizations costs	$12,784 (36,137)	$15,865 (35,729)	$15,061 (35,808)
Total ED visits costs	$813 (2337)	$726 (1806)	$749 (1955)
Other outpatient medical costs	$74,941 (65,794)	$99,371 (126,094)	$92,995 (113,901)
Total office visit costs	$24,917 (26,402)	$23,630 (29,480)	$23,965 (28,676)
Medical cancer-related costs	$46,514 (47,480)	$53,400 (51,101)	$51,603 (50,204)
Medical non-cancer-related costs	$42,025 (55,698)	$62,562 (105,513)	$57,202 (95,412)

feasible; although, for atypical disease and low-grade NET with high tumor burden, chemotherapy may be used initially[3,7,8,11]. The NCCN SCLC guidelines in place during the time of this study recommended TT or CC for most patients with lung NET, reserving SSA for patients with positive octreotide scans or carcinoid syndrome[7,8]. Thus, it may be that physicians treating lung NET more often followed the NCCN SCLC guidelines than NCCN NET guidelines. In addition, patients may have had a pathologic finding suggesting chemotherapy was a better choice (e.g. high Ki-67, high mitotic index), but data limitations and privacy restrictions make such information not obtainable for our sample. The high percentage of patients treated with chemotherapy may indicate our study population was predominately comprised of patients with poorly differentiated NETs. Lastly, clinicians may be unfamiliar with NCCN recommendations, or may not choose to treat in accordance with NCCN guidelines, although, again, our study provides no direct support for this hypothesis.

In studies of patients with breast, lung, colorectal, and prostate cancer, cost decreases over time[12–14]. In the small group of patients for whom 2 years of data were available in the current study, trends in utilization and cost over time were mixed. The decrease in costs among patients initiating CC is consistent with the larger body of literature (although the current study focused on the year following initial

Table 5. Annual healthcare resource utilization and cost in years 1 and 2 among patients with 2-year post-index continuous enrollment.

	Somatostatin analogs (SSA)	Cytotoxic Chemo (CC)
n	49	114
No. of office visits, mean (SD)		
Y1	22.6 (11.0)	31.3 (22.3)
Y2	21.7 (13.2)	18.6 (15.7)
No. of inpatient hospitalizations, mean (SD)		
Y1	0.55 (1.35)	0.54 (0.94)
Y2	0.78 (1.23)	0.34 (0.93)
Total costs, mean (SD)		
Y1	$97,301 (72,952)	$95,696 (89,824)
Y2	$105,411 (119,251)	$52,670 (67,635)

pharmacotherapy, not diagnosis, as in prior studies), but costs were slightly higher in the second year for SSA initiators. We grouped patients by their initial utilization; patients that began treatment with SSA in year 1 may have changed therapy in subsequent years, and these changes in treatment could be responsible for the observed cost increase. This group contained fewer than 50 patients, so a small number of outliers could also explain this finding.

Limitations

This study had limitations. First, findings may not reflect the non-commercially insured US population, because commercially insured patients may differ from the general population. The sample did not include older adults $\geq$65 years old, and many patients with lung NET are in this category. The vast majority of US patients over 65 are covered by Medicare, and their data are not available in this privately-insured sample. Second, the administrative claims used in this study were collected for reimbursement purposes, and the completeness and accuracy of medical coding is subject to data coding restrictions and data entry error. Furthermore, treating NET is complex and clinical decision-making is determined by location, tumor markers, extent of disease, and other factors. Our data did not include this level of detail. Specifically, while lung NET can be identified by using a list of ICD-9-CM codes, the presence of advanced disease must be inferred by observing the use of pharmacologic treatment. Similarly, there is no information on tumor markers, nor are pathology reports available. Third, the healthcare cost estimates may be under-estimated, as services not covered by insurance or rendered "out-of-network" would not have been included. Cost estimates include direct healthcare costs only, and do not take into account important indirect costs associated with caregiver burden, loss of productivity, or reduced quality-of-life. Our study cohort was identified based upon initiation of pharmacologic treatment, and included all costs after treatment initiation. However, some patients may have had certain treatments, such as liver-directed therapy, before initiating pharmacologic therapy. In this case we would not have included the cost of liver-directed therapy in our total cost estimate. Patients who had liver-directed treatment as their only therapy (and had no follow-on pharmacologic treatment) would not have been included in our study. Fourth, this study presents descriptive results only and is not intended to compare the therapies examined. A larger, more clinically detailed study would be required to make valid comparisons.

Conclusions

This study, for the first time, assessed treatment adherence, resource utilization, and costs among patients with lung NET. In this descriptive study, over two-thirds of patients with lung NET initiate treatment with cytotoxic chemotherapy. The utilization and costs were overall significant, and trends of costs over time were mixed. Additional research with a larger sample size would be needed for adjustment of between-group differences.

Transparency

Declaration of funding

Funding for this study was provided by Novartis Pharmaceuticals Corporation.

Author contributions

All authors were equally involved in the conception and design of the study. Eunice Chang conducted the statistical analyses and all authors contributed equally in the interpretation of data, drafting of the manuscript, and critical revisions for intellectual content. All authors approve of the final version to be published and agree to be accountable for all aspects of the work.

Declaration of financial/other relationships

B.C. is an employee and shareholder of Novartis Pharmaceuticals Corporation. A.B.B. is an employee of Northwestern University and was paid by Novartis to consult as a subject matter expert. A.B.B. declares grant funding from Acerta, Celgene, Advanced Accelerator App., Novartis, Infinity Pharmaceuticals, Merck Sharp & Dohme, Taiho Pharmaceuticals, Bristol-Myers Squibb, Medimmune/AstraZeneca, Xencor; consultancy for Genentech/Roche, Bristol-Myers Squibb, Celgene, Taiho, Boehringer Ingelheim, EMD Serono, Integragen, Guardant, Opsona Therapeutics, Lexicon, Novartis, Boston Biomedical, Helsinn, Guerbet, Eli Lilly, TRM Oncology, Immunogen, Pfizer, Exelixis, Oncosil Medical, Purdue Pharma, Halozyme Therapeutics, AstraZeneca, Rafael Pharmaceuticals. M.S.B., E.C. and T.Y. are employees of Partnership for Health Analytic Research, LLC (PHAR, LLC), a health services research company paid by Novartis to conduct this research. CMRO peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Previous presentations

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