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Severe adverse events impact overall survival and costs in elderly patients with advanced non-small cell lung cancer on second-line therapy

Hossein Borghaei[a,*], Yeun Mi Yim[b], Annie Guerin[c], Irina Pivneva[c], Sherry Shi[c], Mayank Gandhi[b], Raluca Ionescu-Ittu[c]

[a] Medical Oncology, Fox Chase Cancer Center, Philadelphia, PA 19111, United States
[b] Genentech, Inc., South San Francisco, CA 94080, United States
[c] Analysis Group, Inc., Montreal, QC, H3B 4W5, Canada

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ABSTRACT

Objectives: Elderly patients with advanced non-small lung cancer (aNSCLC) represent a high-risk patient population due to disease burden, comorbidities, and performance status, particularly after progressing on first-line therapy. Among elderly patients who receive second-line therapy, treatment related toxicities can have substantial impact on both clinical and economic outcomes. This study assessed the impact of severe adverse events (AEs) during second-line therapy on overall survival (OS) and all-cause heathcare costs in elderly with aNSCLC.

Materials and methods: Patients with aNSCLC aged ≥65 years who initiated second-line chemotherapy/targeted therapy were identified in the SEER-Medicare database (2007–2011). Fifty-seven AEs were identified by literature review and consultation with two oncologists. Severe AEs were defined as AEs that required a hospitalization and were operationalized based on AE diagnosis(es) recorded during hospitalizations. OS post-second-line initiation and healthcare costs during second-line were compared between patients with and without severe AEs.

Results: Among 3967 patients initiating second-line therapy, 1624 (41%) had ≥1 severe AE, where hypertension (26%), anemia (24%), and pneumonia (23%) were most commonly reported. Patients with and without severe AEs had similar demographic and cancer characteristics at diagnosis and similar second-line treatment regimens, but patients with severe AEs had more comorbidities at second-line initiation. Median OS was lower in patients with versus without severe AEs (6 vs. 11 months). After multivariate adjustment, hazard of death was more than twice higher in patients with versus without severe AEs (adjusted hazard ratio [HR] 2.31, 95% CI 2.16–2.47). Healthcare costs were more than twice higher in patients with versus without severe AEs ($16,135 vs. $7559 per-patient-per-month).

Conclusion: Severe AEs among elderly patients with aNSCLC treated with second-line chemotherapy/targeted therapy were found to be associated with decreased OS and increased healthcare costs. Results suggest a potential link between severe AEs in second-line treated aNSCLC elderly and patient survival and economic burden to the healthcare system.

1. Introduction

Lung cancer is a costly disease that accounts for a quarter of all cancer deaths in the United States (US) [1]. In 2010 in the US, lung cancer had an estimated medical cost of $12.1 billion [2]. About 85% of all lung cancer cases have non-small cell histology [3] and most patients are diagnosed in advanced stages of the disease [4]. Treatment advancements over the past 30 years have almost doubled the survival of patients with advanced non-small cell lung cancer (aNSCLC) [5], but progression-free survival remains low (3–5 months) [6–9]. Second-line therapy has been shown to prolong survival for patients who progress on frontline therapy as compared to best supportive care [10], although some patients experience a decline in functional status during frontline therapy that limits their tolerability for a second line of therapy.

Abbreviations: AE, adverse event; ALK, anaplastic lymphoma kinase; aNSCLC, advanced non-small cell lung cancer; DRG, diagnosis-related group; EGFR, epidermal growth factor receptor; GLM, generalized linear model; HMO, health maintenance organization; HR, hazard ratio; ICD-9, international classification of diseases ninth edition; OS, overall survival; PD-L1, programmed death-ligand 1; PPPM, per patient per month; SEER, Surveillance, Epidemiology, and End Results

* Corresponding author at: Fox Chase Cancer Center, 333 Cottman Avenue, Philadelphia, PA 19111, United States.
E-mail addresses: hossein.borghaei@fccc.edu (H. Borghaei), yim.yeun@gene.com (Y.M. Yim), annie.guerin@analysisgroup.com (A. Guerin), irina.pivneva@analysisgroup.com (I. Pivneva), sherry.shi@analysisgroup.com (S. Shi), gandhi.mayank@gene.com (M. Gandhi), raluca.ionescu-ittu@analysisgroup.com (R. Ionescu-Ittu).

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Nevertheless, approximately half of patients who progress on frontline therapy do continue with a second line [11,12]. The standard of care in second-line therapy has long included docetaxel, pemetrexed, and other cytotxic chemotherapy [13], but the treatment landscape is currently evolving towards immune checkpoint inhibitors (e.g., anti- programmed death-1 [PD-1] and anti PD-L1 inhibitors) and new biomarker-directed agents (e.g., anaplastic lymphoma kinase [ALK]-inhibitors and next generation anti-epidermal growth factor receptor [EGFR] agents) in select populations and primarily in the frontline setting [14]. However, little is known on the clinical and economic outcomes associated with second-line therapy, especially among the elderly who represent the majority of the patients with aNSCLC [1] and pose many challenges in the selection of optimal treatment [15]. Specifically, due to their co-morbid conditions and possibly poor performance status and high disease burden, elderly patients are at increased risk of adverse events (AEs) that may reduce their survival by being potentially life-threatening themselves and/or by interfering with the course of the anti-cancer therapy. AEs that require hospitalizations or additional medical encounters, tests, or treatments are also likely to translate into higher healthcare costs. While some data are available on clinical outcomes in patients with aNSCLC treated with second-line therapies, most studies were clinical trials focusing on specific second-line regimens in patients with good performance status and their results may not be generalizable to the general population of elderly patients with aNSCLC. To the best of our knowledge, economic outcomes beyond first-line therapy have never been studied in elderly patients in the US.

Using a cohort of elderly patients diagnosed with aNSCLC from 2007 to 2011 who were initiated on second-line therapy as part of their routine care, the current study aimed to assess the impact of severe AEs during second-line therapy on 1) overall survival (OS) and 2) healthcare costs incurred during second-line therapy.

2. Materials and methods

2.1. Data sources

This study used the SEER-Medicare data, which comprises 2 large population-based databases linked at the patient level: the US National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) registry and the Medicare claims database. The SEER includes demographics and cancer characteristics (e.g., the cancer site, stage, histology) at the time of diagnosis for all cancer cases diagnosed from 1973 to 2011 across 20 US geographic areas covering approximately 30% of the US population. The Medicare-linked database contains claims related to hospital care (part A), outpatient medical services (part B), and outpatient drug prescriptions (part D) from 2007 to 2013 as well as the date of death of patients aged ≥65 years in the SEER, allowing a comprehensive assessment of treatments, health resource utilization, healthcare costs, treatment-related AEs, and patient survival.

2.2. Study design and study cohorts

The study used a retrospective cohort design (**Supplementary** Fig. 1). The study sample included patients aged ≥65 years diagnosed with pathologically confirmed aNSCLC (stages IIIB or IV) regardless of histology between 2007 and 2011 who were continuously enrolled with Medicare Parts A and B for ≥6 months before the aNSCLC diagnosis and with Parts A, B, and D for ≥4 months after the aNSCLC diagnosis and had initiated second-line therapy regardless of the agents used (Fig. 1). The start and end dates of first- and second-line regimens were identified from the patterns of treatment observed in the Medicare claims data, based on an algorithm adapted from previously published claims-algorithms [16–19] (**Supplementary** Fig. 2). Patients enrolled in a health maintenance organization (HMO; i.e., for which complete cost information may not be available) ≥6 months before and ≥4 months after the aNSCLC diagnosis and those enrolled in a clinical trial were excluded. Severe AEs (i.e., defined as AEs that required a hospitalization and operationalized based on AE diagnoses recorded during hospitalizations [20,21]) were documented based on a list of 57 potential AEs identified by a review of the literature on possible AEs of chemotherapy in NSCLC and other cancers [17] and also by consultation with two oncologists (**Supplementary** Table 1). Patients in the study sample were stratified into two cohorts: 1) patients with one or more severe AEs during second-line therapy, and 2) patients without any severe AE during second-line therapy. Patients were followed from the initiation of second-line therapy to the end of continuous Medicare Parts A/B/D enrollment, beginning of HMO enrollment, death, or end of data availability (12/31/2013), whichever occurred first.

2.3. Outcomes and measurements

Study outcomes included OS, defined as the time from the initiation of second-line therapy to death from any cause, and all-cause healthcare costs incurred during the course of second-line therapy. All cause healthcare costs were categorized into medical service costs and pharmacy costs, where medical service costs included 1) treatment-related costs, including provider fees for the administration of anti-cancer therapies, such as chemotherapy, targeted therapy, radiation therapy or supportive care, and the associated cost of the drug, and 2) non-treatment-related costs included emergency room visits, inpatient and outpatient care, home care, hospice, skilled nursing facility, durable medical equipment, and other healthcare services. Costs were reported from a Medicare payer perspective as both (a) mean costs per patient over the entire duration of second-line therapy and (b) costs per patient per month (PPPM) of second-line therapy. Costs were adjusted to 2014 US dollars. Patients characteristics are listed in Table 1.

2.4. Statistical analyses

Patient characteristics were compared between the study cohorts using Wilcoxon rank-sum tests (continuous variables) and Chi-square tests (categorical variables). OS rates at 3, 6, and 12 months and median OS after the initiation of second-line therapy were estimated using Kaplan-Meier analyses. Unadjusted OS was compared between study cohorts using log-rank tests. Adjusted OS was compared between study cohorts using multivariate Cox proportional-hazards regression model in which the occurrence of the first severe AE during second-line therapy was treated as a time-dependent covariate to account for the time when the first severe AE occurred during the follow-up. All other covariates were measured at second–line therapy initiation and treated as fixed covariates. Fixed covariates included age, sex, Charlson comorbidity index, and cancer stages as de facto covariates while additional patient characteristics were selected based on statistical significance through backward selection.

The incremental impact of severe AEs on the all-cause healthcare costs incurred during second-line therapy was estimated using multivariate two-part regression models, where the first part was a logistic model with a binomial distribution modeling probability of a zero cost and the second part was a generalized linear model (GLM) with a log link and a gamma distribution. P-values and 95% CIs for the cost differences between cohorts were estimated using non-parametric bootstrap re-sampling with 499 replications.

3. Results

3.1. Patient characteristics

The study sample included 3967 patients with aNSCLC who initiated second-line therapy, representing 61.2% of the patients who ended first-line therapy and 20.4% of the patients diagnosed with

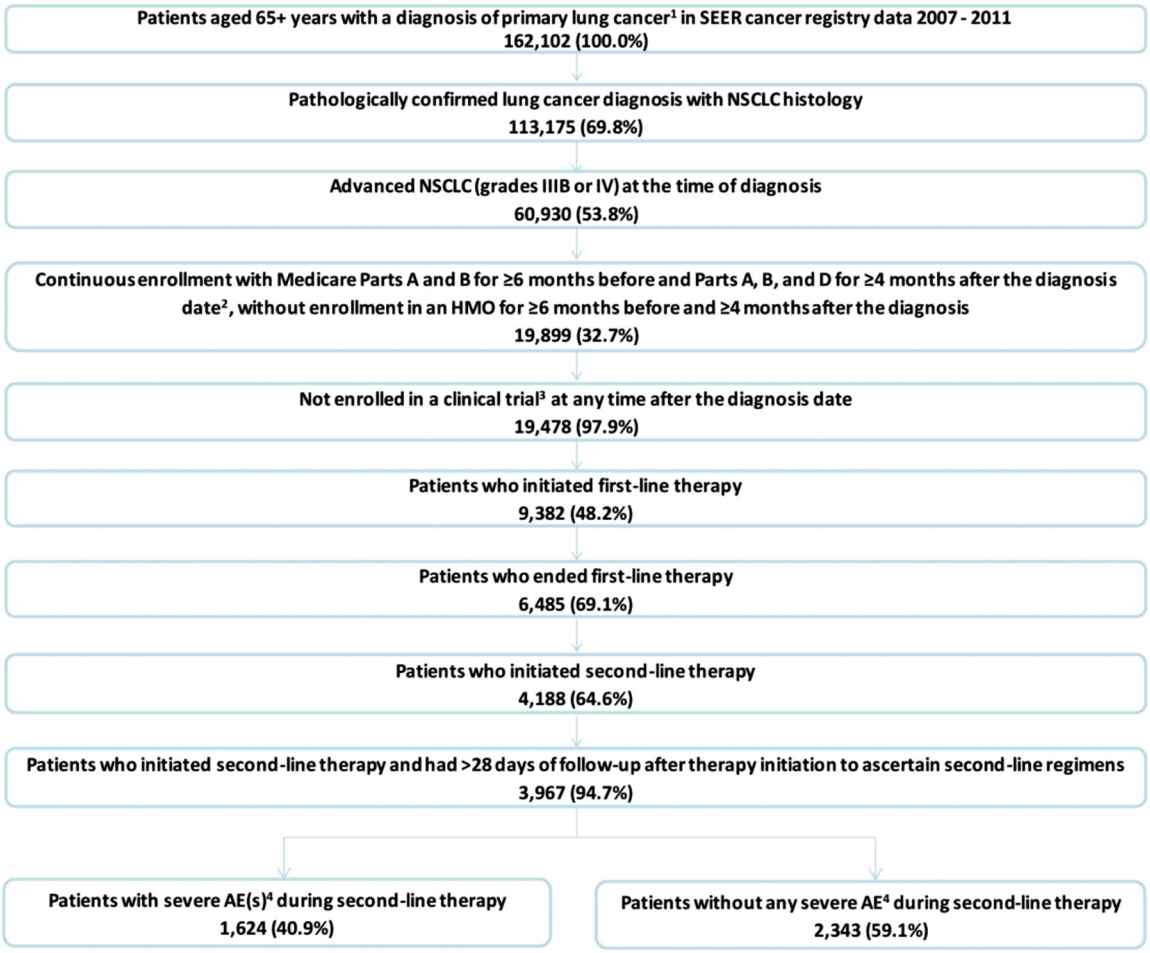

Fig. 1. Sample selection flowchart.
aNSCLC: Advanced non-small cell lung cancer; HMO: Health maintenance organization; NSCLC: Non-small cell lung cancer; SEER: Surveillance, Epidemiology, and End Results.
[1]ICD-O-3 site codes C340–C349.
[2]For patients who died within 4 months of diagnosis, enrollment criteria are required from index date until death.
[3]ICD-9 code: V70.7.
[4]Patients with at least one AE requiring a hospitalization during second-line therapy. The list of AEs assessed is presented in Online Table 1.

aNSCLC (Fig. 1). Severe AEs during second-line therapy were observed for 1624 (40.9%) of the patients in the study sample. Most common severe AEs observed during second-line therapy included hypertension (26%); anemia (24%); pneumonia, pneumonitis and/or interstitial lung disease (23%); dyspnea (23%); and chronic airway obstruction (21%; **SupplementaryTable 1**). While almost all patients with severe AEs experienced multiple types of severe AEs (98.5%; median 7 distinct AEs/patient), these were recorded during a single inpatient stay for more than two-thirds of the patients (**SupplementaryTable 1**).

At initiation of second-line therapy, patients with severe AEs during second-line therapy had similar demographic and cancer characteristics to the patients without severe AEs (mean age 73 years, approximately half males, about two-thirds with stage IV NSCLC, and about one-half with adenocarcinoma histology), but higher comorbidity burden (mean Charlson Comorbidity Index [22]: 8.3 vs. 7.8, $p < 0.01$; Table 1).

While radiotherapy use was more common among the patients who experienced severe AEs during the second-line therapy as compared to those who did not, pharmacological second-line regimens were similar between the two study cohorts, with pemetrexed monotherapy, erlotinib monotherapy, and taxane therapy being the most commonly used regimens in both cohorts (Table 1).

3.2. OS after the initiation of second-line therapy

In the full study sample, median OS after the initiation of second-line therapy was 8 months and the 1-year OS rate was 37.6%. OS was significantly shorter for patients with severe AEs during second-line therapy than patients without severe AEs, in both unadjusted analyses (median OS: 5.5 vs. 10.5 months; 1-year OS rates: 26.0% vs. 45.7%; log-rank $p < 0.01$) and adjusted analyses (HR for mortality = 2.31; $p < 0.01$; Fig. 2).

3.3. All-cause healthcare costs during the course of second-line therapy

The mean all-cause healthcare total cost over the entire duration of second-line therapy was $37,687 for the full study sample; $50,795 (median: $36,644) for patients with severe AEs and $28,601 (median: $17,819) for those without. This difference in all-cause healthcare cost between the study cohorts was largely driven by differences in inpatient costs ($18,342 vs. $127), but other cost components were also higher among patients with severe AEs during second-line therapy (e.g., pharmacy costs: $9137 vs. $6440; skilled nursing facility: $1102 vs. $71; home care costs: $1604 vs. $405; Fig. 3).

When the healthcare costs were indexed to the duration of the second-line therapy, similar patterns were observed, with double mean all-cause healthcare costs PPPM for patients with severe AEs as compared to patients without severe AEs ($16,135 vs. $7559; Table 2; medians: $13,582 vs. $6932, respectively). After adjustment for potential confounding factors, the mean cost difference PPPM between patients with and without severe AEs during second-line therapy was

Table 1
Characteristics with advanced NSCLC treated with L2 therapy: comparison patients with and without severe AEs on L2.

	Patients With Severe AEs during Second-line Therapy	Patients Without Severe AEs during Second-line Therapy	P-value
	N = 1624	N = 2343	
Demographics			
Age, year, mean ± SD [Median]	73.6 ± 5.7 [73.0]	73.3 ± 5.6 [73.0]	0.05*
Male, N (%)	827 (50.9)	1136 (48.5)	0.13
Race/ethnicity, N (%)			
Non-Hispanic White	1301 (80.1)	1913 (81.6)	0.23
Non-Hispanic Black	162 (10.0)	173 (7.4)	≤0.01*
Asian	93 (5.7)	135 (5.8)	0.96
Hispanic	24 (1.5)	48 (2.0)	0.19
Other[a]	44 (2.7)	74 (3.2)	0.45
Marital status, N (%)			
Never married	143 (8.8)	207 (8.8)	0.97
Married	860 (53.0)	1292 (55.1)	0.17
Widowed/Divorced/Separated	580 (35.7)	769 (32.8)	0.06
Unmarried or domestic partner	NR	NR	NR
Unknown/other (< 1%)	41 (2.5)	75 (3.2)	0.20
Index of poverty[2], N (%) (percent residents living below poverty line in the ZIP code where patient resides)			
< 20	1269 (78.1)	1838 (78.5)	0.76
≥20	344 (21.2)	474 (20.2)	0.47
Unknown	11 (0.7)	31 (1.3)	0.05
Index of lower education,[b] N (%) (percent residents with < 12 grades in the ZIP code where patient resides)			
< 20	1172 (72.1)	1724 (73.6)	0.30
≥20	389 (24.0)	539 (23.0)	0.49
Unknown	63 (3.9)	80 (3.4)	0.44
SEER registry where the patient was captured, N (%)			
Greater California	254 (15.6)	470 (20.1)	≤0.01
New Jersey	269 (16.6)	300 (12.8)	≤0.01
Others (< 10%)	1101 (67.8)	1573 (67.1)	0.64
Cancer characteristics at primary diagnosis			
AJCC 6 stage, N (%)			
IIIB	508 (31.3)	747 (31.9)	0.69
IV	1116 (68.7)	1596 (68.1)	0.69
Tumor size,[c] mm, mean ± SD [Median]	45.2 ± 24.1 [40.0]	43.7 ± 23.9 [40.0]	0.03*
Categories, N (%)	–	–	–
≤20 mm	133 (8.2)	223 (9.5)	0.15
20–50 mm	627 (38.6)	979 (41.8)	0.05*
≥50 mm	486 (29.9)	626 (26.7)	0.03*
Unknown	378 (23.3)	515 (22.0)	0.34
~~NSCLC histology,~~ N (%)	1899 (31.0)	2090 (30.9)	0.92
Adenocarcinoma, NOS	861 (53.0)	1335 (57.0)	0.01*
Adenosquamous	22 (1.4)	20 (0.9)	0.13
Squamous cell carcinoma	405 (24.9)	559 (23.9)	0.44
Other[d]	50 (3.1)	64 (2.7)	0.56
NSCLC, NOS[e]	286 (17.6)	365 (15.6)	0.09
SEER indicator of distant metastases[f] at diagnosis, N (%)			
Yes	1169 (72.0)	1662 (70.9)	0.47
Year of diagnosis, n (%)			
2007	336 (20.7)	456 (19.5)	0.34
2008	310 (19.1)	472 (20.1)	0.41
2009	330 (20.3)	473 (20.2)	0.92
2010	338 (20.8)	464 (19.8)	0.44
2011	310 (19.1)	478 (20.4)	0.31
Baseline comorbidity profile			
CCI Score, mean ± SD [Median]	8.3 ± 2.5 [8]	7.8 ± 2.4 [8]	< 0.01*
Physical comorbidities, N (%)			
Hypertension	1337 (82.3)	1808 (77.2)	< 0.01*
Anemia	1126 (69.3)	1402 (59.8)	< 0.01*
Fluid and electrolyte disorders	810 (49.9)	1072 (45.8)	0.01*
Bleeding	565 (34.8)	724 (30.9)	0.01*
Diabetes	552 (34.0)	687 (29.3)	≤0.01*
Peripheral vascular disease	521 (32.1)	655 (28.0)	≤0.01*
Weight loss	438 (27.0)	477 (20.4)	< 0.01*
Congestive heart failure	398 (24.5)	406 (17.3)	< 0.01*
Mental comorbidities, N (%)			
Mood disorders[g]	397 (24.4)	544 (23.2)	0.37
Other conditions[h]	422 (26.0)	486 (20.7)	< 0.01*

(*continued on next page*)

Table 1 (*continued*)

	Patients With Severe AEs during Second-line Therapy	Patients Without Severe AEs during Second-line Therapy	P-value
	N = 1624	N = 2343	
Therapies			
Pharmacological second-line regimens, N (%)			
Chemotherapy-based regimens (no targeted agent)	1080 (66.5)	1528 (65.2)	0.59
Pemetrexed	308 (19.0)	445 (19.0)	0.98
Taxanes	148 (9.1)	219 (9.3)	0.80
Gemcitabine	133 (8.2)	140 (6.0)	≤0.01*
Platinum + taxanes	132 (8.1)	226 (9.6)	0.10
Gemcitabine + platinum	91 (5.6)	120 (5.1)	0.51
Other regimens (each used by < 5% pts in the cohort)	268 (16.5)	378 (16.1)	0.76
Targeted therapy-based regimens (at least one targeted agent)	544 (33.5)	815 (34.8)	0.59
Erlotinib	276 (17.0)	405(17.3)	0.81
Other regimens (each used by < 5% pts in the cohort)	268 (16.5)	410 (17.5)	0.41
Non-pharmacologic therapies prior to or concurrently with second-line, N (%)			
Radiation therapy	1007 (62.0)	1345 (57.4)	≤0.01*
Tumor-removal surgery	323 (19.9)	495 (21.2)	0.34
Status at the end of follow-up, N (%)			
Ended the second-line therapy before the end of follow-up[i]	868 (53.5)	1946 (83.1)	< 0.01*
Died on second-line therapy	266 (16.4)	82 (3.5)	< 0.01*
Data availability ended during second-line therapy	490 (30.2)	315 (13.4)	< 0.01*
Among patients who ended the second-line therapy			
Duration of second-line therapy, months, Mean ± SD [Median]	4.6 ± 5.6 [3.0]	3.7 ± 3.7 [2.7]	< 0.01*
Initiated third-line therapy, N (% out of those who completed second-line therapy)	501 (57.7)	1426 (73.3)	< 0.01*

IQR: interquartile range. AE: adverse events; AJCC 6: 6th edition of the American Joint Committee on Cancer Staging Manual; CCI: Charlson comorbidity score; NR: Not reported (categories with less than 0.05 proportion were not reported); NR: Not reported. Per data user agreement with the National Cancer Institute exact count cannot be reported for cell sizes with > 11 patients.

* Statistically significant at $p < 0.05$.

[a] Includes Native Americans, other, and unknown ethnicities.

[b] Estimated from the American Community Survey (ACS) 2008–2012; the ACS was used in place of the 2010 Census files because detailed demographic, social, economic, and housing data are no longer collected as part of the decennial census; the data that were collected in previous SEER-Medicare data cuts from the Census long form sample are now produced from the American Community Survey.

[c] Four outliers with tumor sizes > 20 cm were reset to a max value of 20 cm.

[d] Includes adenoid cystic carcinoma and mucoepidermoid carcinoma, carcinosarcoma, giant cell carcinoma, large cell carcinoma, pleomorphic carcinoma, NOS, pulmonary blastoma, and spindle cell carcinoma.

[e] A non-specific histology code is used in the SEER database when the cancer registry abstractor did not find enough information (e.g., test results) to confirm with certitude the specific cancer histology (patients may have any specific histologies).

[f] Could include malignant pleural effusion; malignant pericardial effusion; extension to contralateral lung, extension to contralateral main stem bronchus, separate tumor nodule(s) in contralateral lung, pleural tumor foci or nodules on contralateral lung; pleural tumor foci or nodules on the ipsilateral lung separate from direct invasion; distant lymph node(s), including cervical nodes extension to skeletal muscle, sternum, skin of chest; abdominal organs, other distant metastases (alone or in combination); could also include "stated as M1a, M1b or M1 (NOS) without additional information on distant metastasis.

[g] Mood disorders included anxiety, bipolar, depressive, dissociative, factitious, and somatoform disorders.

[h] Other conditions included psychological factors affected or determined by physical condition and those that may be a focus of clinical attention, including psychological factors affecting medical condition, and medication-induced movement disorders, among others.

[i] Patients who ended second-line therapy and started a third-line therapy, or patients who ended second-line therapy and remained untreated for > 45 days.

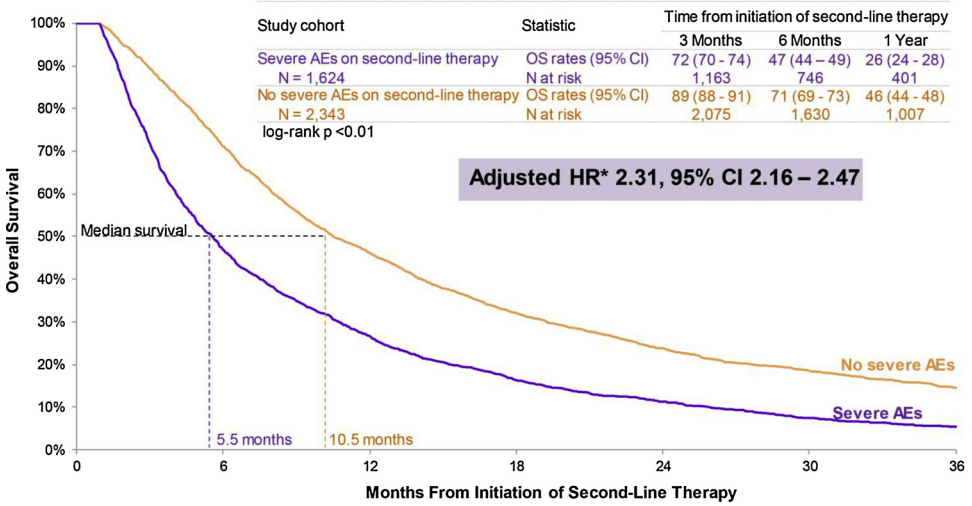

Fig. 2. Comparison of OS between patients with and without severe AEs during second-line therapy.
*Patients with versus without severe AEs on second-line therapy.

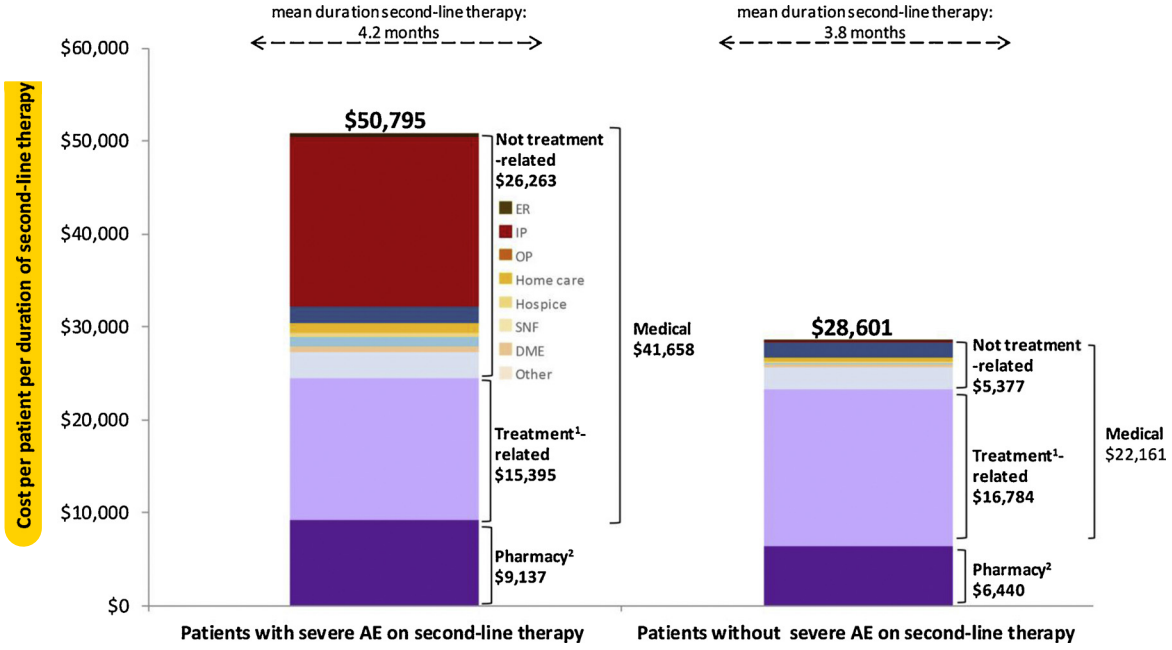

Fig. 3. All-cause healthcare costs per patient over the entire duration of second-line therapy, by cost component.

Table 2
Incremental impact of severe AEs on all-cause healthcare costs during second-line among patients with aNSCLC treated with second-line therapy.

	All-Cause Costs Incurred During Second-line Therapy (2014 USD)[a] Per Patient Per Month of Second-line Therapy			
	Mean ± SD		Adjusted Cost Difference[b,c]	
	Patients with Severe AE during Second-line Therapy N = 2343	Patients Without Severe AE during Second-line Therapy N = 1624	With vs. Without Severe AE during Second-line Therapy (95% CI)	P-value[d]
Total costs[e]	16,135 ± 10,297	7559 ± 4062	8588 (8064–9063)	≤0.01*
Medical service costs[f]	14,550 ± 10,322	6158 ± 4437	8473 (7919–9026)	≤0.01*
Treatment-related[g]	4118 ± 3807	4468 ± 4061	−288 (−539 to −33)	0.02*
Not treatment-related	10,433 ± 9830	1691 ± 1698	8752 (8216–9189)	≤0.01*
Emergency room costs	114 ± 291	65 ± 247	50 (33–66)	≤0.01*
Inpatient costs	7988 ± 9246	74 ± 850	7895 (7396–8306)	≤0.01*
Outpatient costs	422 ± 560	473 ± 667	−50 (−87 to −11)	≤0.01*
Home care costs	337 ± 628	160 ± 502	172 (137–207)	≤0.01*
Hospice costs	271 ± 1068	104 ± 537	158 (107–208)	≤0.01*
Skilled nursing facility costs	456 ± 1636	32 ± 536	411 (334–496)	≤0.01*
Durable medical equipment costs	143 ± 369	90 ± 358	56 (36–78)	≤0.01*
Other medical service costs[h]	702 ± 698	693 ± 693	17 (−22 to 57)	0.06
Pharmacy costs	1585 ± 2493	1401 ± 2152	177 (26–313)	0.27

* Statistically significant at $p < 0.05$.

[a] Healthcare costs were calculated from medical and pharmacy claims, adjusted for inflation using the Consumer Price Index for medical components, and expressed in 2014 USD during the second-line therapy.

[b] Incremental costs were estimated using a generalized linear model (GLM) with two-part models, for which the first part was a logistic model with a binomial distribution and the second part was a GLM with a log link and a gamma distribution.

[c] Adjusted models controlled for demographics (age, sex, and SEER registry state), AJCC 6 stage, CCI score at the initiation of second-line therapy, and presence of physical and mental comorbidities between the diagnosis and the initiation of second-line therapy.

[d] Adjusted p-values were estimated using non-parametric bootstrap re-sampling techniques of 500 iterations.

[e] Total costs included total medical service costs and pharmacy costs.

[f] Total medical service costs included emergency room costs, home care costs, hospice costs, inpatient costs, outpatient costs, skilled nursing facility costs, and other medical service costs.

[g] Chemotherapy, targeted therapy, radiation therapy or supportive care therapy (i.e., growth factors, antiemetic, antianemia and corticosteroids); includes both the cost of the drugs (where applicable) and provider fees for treatment administration. In the event a treatment was administered during an inpatient stay, it is possible that the cost for the treatment administration was not reported individually; therefore it was reported as zero in this analysis. This may result in an underestimation of the treatment-related cost; however, the cost of that treatment would be captured in the inpatient cost − therefore, the total cost estimate would still be accurate.

[h] Other medical costs included institutional outpatient claims with services spanning > 3 days, and non-institutional claims not occurring within any inpatient/skilled nursing facility admission or emergency room/outpatient visit.

$8588 ($p < 0.01$) and the cost component with the largest adjusted cost difference between the study cohorts remained the inpatient costs (adjusted cost difference $7895 PPPM, $p < 0.01$).

4. Discussion

Despite representing the majority of patients diagnosed with aNSCLC, elderly patients were generally excluded from clinical trials due to disease burden, comorbidities, and performance status [23]. Yet, elderly patients with high disease burden and poor performance status might be at highest risk of experiencing severe AEs related to the cancer-directed therapy, especially after failing first-line therapy. To ensure these vulnerable patients receive optimal care, it is important to understand to what extent they experience therapy-related severe AEs and whether there is a potential link with the survival and healthcare costs. By providing data on a large sample of the US elderly with aNSCLC managed in "real world" practice across multiple health care delivery settings and diverse geographic regions, the SEER-Medicare database provided a unique opportunity to provide an answer to these questions.

Using SEER-Medicare data, the current study showed that only one in two elderly patients diagnosed with aNSCLC receive first-line therapy and only one in five receive second-line therapy (48.2% and 20.4%, respectively). Among those treated with second-line therapy, severe AEs requiring hospitalizations were common. Furthermore, most patients who had an AE-related hospitalization experienced multiple AEs during the hospitalization. The study also showed that the hazard of death of patients with severe AEs during second-line therapy was more than twice higher than that of patients without severe AEs (adjusted HR = 2.31, $p < 0.01$; median OS: 5.5 vs. 10.5 months; 1-year OS rates: 26.0% vs. 45.7%) and that patients with severe AEs had double all-cause healthcare costs during the second-line therapy as compared to patients without severe AEs during second-line therapy ($16,135 vs. $7559 PPPM, adjusted cost difference $8588; $p < 0.01$).

The most commonly observed severe AE was hypertension (26%). Although it was defined as an AE within the context of the current study, it might also, in part, reflect a commonly occurring comorbidity among the elderly as it is difficult to identify incident cases of hypertension in claims data to distinguish hypertension as a severe AE from hypertension as a commonly occurring comorbidity among the elderly.

To the best of our knowledge, no study to date has compared clinical or economic outcomes between patients with and without severe AE during second-line therapy for aNSCLC. A few previous US studies investigated OS and costs among patients with aNSCLC treated with second-line therapy and their results appear to be largely consistent with those from the current study despite differences in study design (e.g., observational claims-based study vs. clinical trials; any second-line regimen vs. specific second-line regimens) and study sample (e.g., elderly patients vs. patients of all ages; patients with any functional status vs. patients with good functional status). With respect to OS, the current study found a 1-year OS rate of 38% after the initiation of second-line therapy, which is in line with the 28–38% range from previous observational studies [24,25] and 27%–38% range from previous randomized controlled trials [26–28]. Similarly, median OS in the current study for the full study sample was 8.3 months versus 7.5 months in an observational study [29] and 6.4–9.5 months in randomized clinical trials [26–28,30,31].

To our knowledge, only two studies to date investigated costs after the initiation of second-line therapy for aNSCLC in the US, both of which focused on patients of all ages in the US. The first study, a retrospective observational study linking electronic medical records of patients with aNSCLC to claims data from 2006 to 2008, reported mean outpatient costs of $3198–$4729 ($4040–$5974 if adjusted to 2014 US dollars) PPPM depending on the second-line regimen (i.e., pemetrexed, docetaxel, or erlotinib monotherapy) [24]. Considering these outpatient costs included the costs of provider-administered chemotherapy ($3342–$4568 in 2014 US dollars [24]) and the costs of supportive care ($206–$671 in 2014 US dollars [24]), they appear to be consistent with the estimates from the current study for treatment-related medical costs ($4118–$4468 PPPM) and not-treatment related outpatient visits ($422–$273). The second study, a retrospective claim database study from 2007 to 2012 among patients with any type of lung cancer, reported mean total costs PPPM of $8281–$16,190 ($8688–$16,985 in 2014 US dollars) and mean inpatient costs of $12,732–$21,790 ($13,357–$22,860 in 2014 US dollars), depending on the second-line regimen received [16], which appear to be higher than the mean total all-cause and inpatient cost from the current study ($11,070 and $3314, respectively, for the full study sample; data not shown). However, the current study measured costs during the second-line therapy (mean 4 months for the full study sample; data not shown), while the previous study measured costs over the 12 months following the initiation of second-line therapy, regardless of when second-line therapy ended, and may have captured inpatient and palliative costs occurring after the failure of second-line therapy.

The results of the current study suggest that severe AEs occurring during second-line therapy might increase the risk of death of elderly patients with aNSCLC. Although the results of the study do not imply a causal link between severe AEs and increased risk of death, there are two likely mechanisms of action that might explain a potential association between them: first, AEs may be themselves life-threatening; second, occurrence of a severe AE might potentially lead to the interruption or discontinuation of treatment, which may have an effect on the risk of tumor progression and survival. The current study also found that severe AEs are common in this population and that most patients who had an AE-related hospitalization, experienced multiple AEs. This finding highlights the vulnerability of elderly patients to AEs [32] and also suggests that AEs can have substantial impact on clinical outcomes. Furthermore, this highlights the importance of taking a total cost of care perspective, as the healthcare cost of elderly patients with aNSCLC does not only include the cost of cancer-directed therapy but also, to a great extent, costs associated with the management of severe AEs of the treatments. Preferential selection of treatments while keeping in mind the safety profile in this population may relate to patients' survival and cost offsets to the healthcare system through reduced hospitalizations. New therapeutic options have better efficacy and tolerability profiles than traditional chemotherapies (e.g., immune checkpoint inhibitors) offering potentially increased treatment options for the elderly population [33–36].

The limitations of this study are inherent to the data source used. First, the study focused on elderly patients and results may not be generalizable to younger patients with aNSCLC. Second, SEER data has a lag of two to four years and, at the time the study was conducted, the data were available only for patients diagnosed before or during year 2011; however, while these patients may have experienced more AEs than patients diagnosed after year 2011, the OS and cost comparison between patients with and without AEs should be minimally affected. Third, the claims-based algorithm used to identify lines of therapy cannot distinguish between switches to a new agent for maintenance therapy versus initiation of a subsequent line. Because maintenance switches are treated as initiations of new therapy lines, the estimates from the current study for clinical and economic outcomes may be conservative. Fourth, most patients experienced multiple AEs concomitantly, limiting the assessment of specific AEs. Furthermore, claims data cannot distinguish between dyspnea, pleural effusion, and chronic airway obstruction that are treatment-associated AEs versus manifestations of lung tumor progression or underlying diseases like chronic obstructive pulmonary disease and emphysema. However, because most patients experience multiple severe AEs during a single hospitalization, the study estimates may only be minimally affected by the potential misclassification of some AEs. Fifth, AE event rates estimated in this study may have been underestimated if there were any inpatient

stays that were reimbursed based on diagnosis-related group (DRG) codes for which not all corresponding ICD-9 codes were recorded in claims data. Finally, inpatient costs are generally not broken down by component, so treatment costs incurred during hospitalizations were likely classified as non-treatment-related inpatient costs.

5. Conclusion

This population-based retrospective study found that the survival of patients with severe AEs during second-line chemotherapy/targeted therapy is lower than that of patients without severe AEs. It also found that there is an economic burden associated with severe AEs. Results suggest a potential link between severe AEs and patient survival in the elderly population and an increased economic burden to the health care system.

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Competing interests statement

HB received consulting fees from Genentech for the current study. YMY and MG are employees of Genentech, Inc. AG, IP, SS, and RII are employees of Analysis Group, a consulting company that received research grants from Genentech for the current study.

Conflict of interest disclosure

Dr. Hossein Borghaei acted as a consultant and advisory board member for BMS, Lilly, Merck, EMD-Serono, Novartis, Pfizer, Astra Zeneca, Genmab, Celgene, Boerhringer-Ingelheim, and Genentech; acted as a data safety monitoring board member for the University of Pennsylvania CART protocols; received honoraria from Celgene; and provided clinical trial support to Millennium, Merck, and Celgene. Yeun Mi Yim and Mayank Gandhi are employees of Genentech, and own stock/stock options. Raluca Ionescu-Ittu, Annie Guerin, Irina Pivneva, and Sherry Shi are employees of Analysis Group, a consulting company that has received research grants from Genentech to conduct this study.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.lungcan.2018.02.011.

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