Lung Cancer 127 (2019) 53–58

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Real-world treatment patterns and outcomes of patients with small cell lung cancer progressing after 2 lines of therapy

Anna D. Coutinho[a], Manan Shah[b,*], Orsolya E. Lunacsek[a], Michael Eaddy[a], Joanne P. Willey[a]

[a] Xcenda, LLC, 4114 Woodlands Parkway, Suite 500, Palm Harbor, FL, 34685, USA
[b] AbbVie Inc., 1 North Waukegan Rd, Dept. GMH1, Bldg. ABV1, North Chicago, IL, 60064, USA

ARTICLE INFO

Keywords:
Small cell lung cancer
Progression-free survival
Overall survival
Real-world
Oncology EMR
Best supportive care

ABSTRACT

Objectives: To evaluate treatment patterns, physician-assessed overall response rate (ORR), progression-free survival (PFS), and overall survival (OS) among third-line (3L)-plus small cell lung cancer (SCLC) patients.
Materials and methods: Retrospective analysis of a United States (US)-based community oncology electronic medical record (EMR) database was conducted. Target sample included SCLC patients ≥18 years of age whose disease progressed after at least 2 prior treatments. Treatment patterns captured systemic therapy and best supportive care (BSC) in 3L, fourth-line (4L), and fifth-line (5L) settings. ORR, PFS, and OS were evaluated for each line of systemic therapy and OS was also evaluated for BSC.
Results: 334 3L SCLC patients received systemic therapy (n = 249) or BSC (n = 85). Mean age (standard deviation [SD]) was 63.7 (9.5), with 72% having extensive disease at initiation of first-line therapy. Of 3L patients, 41% and 12% went on to 4L and 5L, respectively. ORR for systemic therapy in 3L and 4L averaged around 21% while 5L was 12%. Median PFS in 3L systemic therapy was 2.3 months (95% confidence interval [CI]: 1.9, 2.5), which decreased in 4L and 5L. Median OS for 3L systemic therapy was 4.4 months (95% CI: 4.0, 5.5), with 6- and 12-month survival rates of 37% and 11%, respectively. In contrast, median OS for 3L BSC was 0.9 months (95% CI: 0.6, 1.2), with 9% survival rate at 6 months.
Conclusion: Current treatments utilized in the 3L-plus setting yield limited survival benefit. Furthermore, patients left untreated and placed on BSC typically live less than 1 month. New therapeutic options are thus needed for these patients, where no approved options exist.

1. Introduction

Approximately 234,030 new cases of lung cancer will be diagnosed in 2018, ~14% of which will be small cell lung cancer (SCLC) [1–3]. SCLC is traditionally staged using the Veterans Affairs Lung Study Group staging system, which divides SCLC patients largely based on the size and spread of the tumor into 1 of 2 stages: limited-stage disease or extensive-stage (ES) disease [4–7]. SCLC presents with an aggressive clinical course, frequently with widespread metastases at diagnosis and, as such, approximately two-thirds of patients have ES disease at diagnosis [8].

SCLC is distinguished from other types of lung cancer by its initial sensitivity to both chemotherapy and radiation therapy [8]. Although sensitive to therapy, the outcomes of newly diagnosed ES SCLC patients are typically poor, with a median progression-free survival (PFS) of 5.5 months, median overall survival (OS) of < 10 months, and 2-year survival rate of < 5% [9,10]. The reason for poor survival in a highly chemosensitive disease population is the rapid development of drug resistance and the failure of second-line and subsequent therapies to affect or slow tumor growth and metastasis [8].

The current standard of care for newly diagnosed ES SCLC is a platinum-doublet-based chemotherapy regimen consisting of cisplatin or carboplatin plus etoposide or irinotecan, which have been the traditional therapy for more than 30 years [9,11]. Combination chemotherapy regimens in first-line patients with ES SCLC result in response rates ranging from 60% to 70% [9,12]; however, almost all patients quickly progress, with a median time to progression ranging from 4 to 7 months. Moreover, only 6%–13% of patients with ES SCLC

Abbreviations: 3L, third-line; 4L, fourth-line; 5L, fifth-line; BSC, best supportive care; CI, confidence interval; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; EMR, electronic medical record; ES, extensive-stage; FDA, Food and Drug Administration; ICD, International Classification of Diseases; IRB, institutional review board; NCCN, National Comprehensive Cancer Network; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PS, performance status; RECIST, Response Evaluation Criteria In Solid Tumors; SCLC, small cell lung cancer; SD, standard deviation; US, United States

* Corresponding author at: Health Economics & Outcomes Research, AbbVie Inc., 1 North Waukegan Rd, Dept. GMH1, Bldg. ABV1, North Chicago, IL, 60064, USA.
E-mail address: manan.shah@abbvie.com (M. Shah).

https://doi.org/10.1016/j.lungcan.2018.11.009
Received 23 July 2018; Received in revised form 2 November 2018; Accepted 7 November 2018

will remain progression-free at 1 year following first-line chemotherapy [13–15].

For those who eventually progress on first-line chemotherapy, clinical trial enrollment is the preferred treatment option per the National Comprehensive Cancer Network (NCCN) SCLC guidelines for second-line and subsequent therapies [9]. Alternative options include palliative care/best supportive care (BSC) or systemic therapy, which is determined based on tumor response to initial therapy and patient performance status [9]. To date, topotecan is the only Food and Drug Administration (FDA)-approved agent for second-line therapy in SCLC patients who were sensitive to front-line chemotherapy (i.e. did not progress within 90 days of completing the regimen), where it confers a 7% overall response rate (ORR), with a median time to progression of 3.8 months and median OS of 6 months [16]. Emerging drugs including 2 immunotherapy agents (nivolumab and ipilimumab) have received breakthrough designation from the FDA and are already available to physicians in the United States (US) based on their inclusion in the NCCN guidelines.

There is no standard treatment for SCLC patients progressing on second-line therapy, and either palliative care/BSC or additional systemic therapy is recommended in lieu of a clinical trial [9,17]. Data regarding the efficacy of systemic therapy in the third-line setting are sparse and mostly limited to small single-institution retrospective reviews or small single-arm trials [18–21]. One international multicenter study evaluating 120 SCLC patients from the United Kingdom, Canada, and Australia in the third-line setting has been published; however, this study did not evaluate outcomes beyond the third-line [22]. Furthermore, no published studies evaluate survival for BSC in the third-line plus setting, making it difficult to determine if systemic therapy improves outcomes in this patient population. In the second-line setting, a phase 3 trial comparing topotecan to BSC showed improved survival and quality of life on chemotherapy, but these results may not translate to the third-line setting [16].

Due to the lack of data on treatment patterns and outcomes in the third-line plus setting of SCLC, a retrospective database study was conducted using electronic medical record (EMR) data from community-based oncology practices in the US to evaluate treatment patterns, physician-assessed ORR, duration of response (DoR), PFS, and OS among SCLC patients whose disease progressed after at least 2 prior treatments.

2. Materials and methods

2.1. Data source

This retrospective cohort study used data captured within the International Oncology Network clinical oncology database from January 1, 2011 through December 31, 2016 (i.e. study period). This EMR database captures outpatient practice encounter data from 350 unique providers across 25 geographically diverse large practices in the US, encompassing more than 650,000 patients. The database includes patient demographic information (e.g. age and gender), laboratory results, diagnoses (e.g. cancer-related and comorbid conditions), disease profile (e.g. stage, anatomic sites of involvement, tumor nodal status, and sites of metastases), treatment plan, specific therapy administrations associated with treatment plans, other medications such as supportive care agents, and performance status. The data elements described above are typically captured through either standardized fields or electronic progress notes. For purposes of this study, electronic progress notes were reviewed to abstract and/or verify information on necessary demographic and clinical characteristics, including histology and performance status (PS). The Social Security Death Index (Social Security Administration's Master Death File) was used to supplement documented vital status. Institutional review board (IRB) waiver for this study was granted by Chesapeake IRB.

2.2. Patient selection

The target sample included SCLC patients ≥18 years of age whose disease progressed after at least 2 prior treatments (1 of which was required to be platinum-based) between February 1, 2011 and September 30, 2016 (i.e. study enrollment period). SCLC identification was based on having at least 1 International Classification of Diseases (ICD) code for lung cancer (ICD-9-CM: 162.2, 162.3, 162.4, 162.5, 162.8, or 162.9; ICD-10-CM: C34.xx) along with histologic confirmation of SCLC within the electronic progress notes of each patient's medical chart. Patients were excluded if they had evidence of any other primary malignancy during the study period.

2.3. Study variables

For eligible patients, study variables were captured through programmatic queries of standardized fields available and/or extracted during the review of electronic progress notes within patient medical charts. Treatment patterns, including BSC, were evaluated from third-line through fifth-line. A new line of therapy was defined as a change in therapy regimen due to progression and not due to toxicity or other reasons. The change in therapy could be a different type of systemic therapy from first-line and second-line or those used again as re-induction. Within each line setting, 2 groups were evaluated: patients initiating active systemic therapy or those initiating BSC. The start of active systemic therapy was defined as the first date of administration. For those receiving active systemic therapy the following metrics were captured: (1) duration of treatment – defined as the time between start date and end date of therapy regimen; (2) treatment-free interval – defined as time to next active systemic therapy; and (3) regimen type. BSC was defined as those patients who stopped receiving active systemic therapy and received supportive care medications/interventions such as oxygen therapy, palliative radiation for pain, medication to treat pain, growth factor support, medication to reduce nausea/vomiting, medication to prevent/treat infection (i.e. antibiotics, antivirals and/or antifungals), medication for anxiety/depression, bisphosphonates, and miscellaneous medications to treat diarrhea, weight loss, edema, breathing problems, and/or constipation. BSC was assumed to start the day after progression. Within the BSC group, a subset of patients deemed to be eligible for active systemic therapy was identified. Eligibility for active systemic therapy was defined as having an Eastern Cooperative Oncology Group (ECOG) PS score of 0 or 1, or if ECOG was unknown, then having at least 30 days of follow-up after the start of BSC.

Physician-assessed ORR was obtained from patients' charts for those initiating active systemic therapy within each line setting. ORR was defined as the percentage of patients having a complete response (CR) or partial response (PR) as documented in the medical charts by the physician. The best response was used to classify patients as having a CR or a PR. Unlike a clinical trial setting where the ORR is defined using Response Evaluation Criteria In Solid Tumors (RECIST) criteria, the ORR in this real-world study was physician-assessed. It is assumed that physicians base their assessment on imaging results, physical examination, or other tests and may implicitly or explicitly be using specific criteria such as RECIST. However, the criteria used to define response are rarely specified in the patient charts. The DoR was calculated among patients with a PR or CR and defined as time from the date of best response to the earliest of the date of progression, death, loss to follow-up, or end of study.

PFS and OS for patients receiving active systemic therapy were calculated as the time between the start of each line of therapy and the earliest of the following dates: (1) date of progression (for PFS only), (2) date of death, (3) loss to follow-up, or (4) study end. Patients without a documented progression event or date of death were censored. For the subgroup initiating BSC with no subsequent active systemic therapy, OS was defined as the time from the day after the date of progression to the

date of death, loss to follow-up, or study end.

2.4. Statistical analysis

Descriptive statistics (percentages, means, medians, and standard deviations [SDs]) were used to describe baseline demographic and clinical characteristics for the SCLC patient sample. Treatment pattern metrics are reported for the subset of patients on active systemic therapy in terms of number and percentage for categorical metrics and means, medians, and SDs for continuous metrics. ORR was reported in terms of number and percentage of patients along with 95% confidence intervals (CIs).

Survival analysis techniques were used to estimate duration of physician-assessed overall response among responders, PFS among patients initiating active systemic therapy, and OS among both patients on active systemic therapy and BSC. For duration of overall response, PFS, and OS, the median duration in months with 95% CIs were reported. Kaplan-Meier curves were obtained for all PFS and OS assessments. All analyses were conducted using SAS version 9.4 (SAS Institute, Inc.).

3. Results

3.1. Patient characteristics

A total of 334 third-line SCLC patients were included in the analysis, of whom 136 went on to fourth-line and 41 went on to fifth-line therapy (Supplementary Fig. 1). The mean age at diagnosis was 64 years, 52% were male, and 72% had ES disease. In those for whom it was documented at diagnosis, 86% had ECOG PS scores of 0 or 1. The majority were smokers with an average weight of 174 pounds (79 kg). Baseline patient characteristics for the full group of 334 patients and for the subgroups of third-line actively treated patients (n = 249) and BSC patients (n = 85) are presented in Table 1.

Table 1
Baseline[a] Characteristics.

	All 3L Patients	3L Active Systemic Therapy Patients	3L BSC Patients
Patient Characteristic	n = 334	n = 249	n = 85
Age in years, mean (SD)	63.7 (9.5)	63.2 (9.4)	64.9 (9.7)
Female, n (%)	160 (47.9)	125 (50.2)	35 (41.2)
Smoking status, n (%)			
Current smoker	142 (42.5)	102 (41.0)	38 (44.7)
Prior smoker (quit)	153 (45.8)	119 (47.8)	34 (40.0)
Never smoked	10 (3.0)	7 (2.8)	3 (3.5)
Unknown	29 (8.7)	21 (8.4)	10 (11.8)
Weight			
Patients with weight available, n (%)	305 (91.3)	220 (88.4)	85 (100)
Weight in pounds, mean (SD)	174.3 (38.9)	176.6 (39.1)	168.4 (37.8)
ECOG, n (%)			
0	59 (17.7)	48 (19.3)	6 (7.1)
1	98 (29.3)	82 (32.9)	19 (22.4)
2	21 (6.3)	16 (6.4)	6 (7.1)
3	4 (1.2)	3 (1.2)	2 (2.4)
Unknown	152 (45.5)	100 (40.2)	52 (61.2)
Stage, n (%)			
Extensive stage	241 (72.2)	171 (68.7)	63 (74.1)
Limited stage	80 (24.0)	64 (25.7)	16 (18.8)
Unknown	13 (3.9)	14 (5.6)	6 (7.1)
Location of metastases, n (%)			
Adrenal glands	36 (10.8)	26 (10.4)	7 (8.2)
Bone	82 (24.6)	61 (24.5)	16 (18.8)
Brain	44 (13.2)	28 (11.2)	15 (17.6)
Contralateral lung	29 (8.7)	18 (7.2)	8 (9.4)
Liver	110 (32.9)	77 (30.9)	29 (34.1)
Lymph nodes	209 (62.6)	157 (63.1)	40 (47.1)
Pericardium	2 (0.6)	1 (0.4)	1 (1.2)
Pleural surface	36 (10.8)	15 (6.0)	7 (8.2)
Other	20 (6.0)	14 (5.6)	5 (5.9)

Key: 3L – third-line; BSC – best supportive care; ECOG – Eastern Cooperative Oncology Group; SCLC – small cell lung cancer; SD – standard deviation.
[a] At first-line treatment initiation.

3.2. Treatment patterns

Almost all of the 334 third-line patients received platinum-based therapy in the first-line setting. In the second-line setting, 49% received topotecan followed by platinum-based therapy (34%) and taxane-based therapy (12%). Within the third-line setting, 75% initiated active systemic treatment and 25% received BSC. The proportion initiating active systemic therapy in fourth and fifth-line was lower but still more than 50% (Table 2). Among actively treated patients, platinum-based regimens were used in only 23% of patients in the third-line setting, with taxane-based regimens the most commonly used type of regimen (29%) followed by use of topotecan as a single-agent regimen (24%) (Table 2). Other single-agent regimens were used by < 6% of patients. In fourth and fifth-line, however, platinum-based regimens were most common (30% and 28%, respectively), followed by taxane-based regimens (21% and 20%, respectively). Treatment with immuno-oncology agents was used by < 10% across all lines of therapy. The average duration of active systemic therapy was 2.1 months in third-line and then decreased in fourth and fifth-line (Table 2). Among patients receiving BSC, more than half were classified as treatment-eligible to receive active treatment as determined by their ECOG status or duration of follow-up available.

3.3. Study outcomes

In this retrospective study of 334 third-line SCLC patients, 25% were either not eligible for, or chose not to receive, active treatment in the third-line setting. The ORR for patients interested and able to receive active systemic therapy in the third and fourth-lines averaged around 21%, while it was 12% for fifth-line therapy. All responses were PRs except for 1 CR in third-line following treatment with carboplatin and etoposide (Table 3). The median DoR in third-line was 2.6 vs 2.0 months in fourth-line. The median PFS in third-line was 2.3 months (95% CI: 1.9, 2.5), 1.9 months (95% CI: 1.6, 2.2) for fourth-line, and 1.7 months (95% CI: 1.3, 3.1) for fifth-line. Survival curves are presented in Fig. 1. Responders (i.e. those with a PR or CR) had a higher median PFS compared to non-responders in third-line (4.3 months [95% CI: 3.7, 5.1] vs 1.9 months [95% CI: 1.7, 2.1]) and fourth-line (2.9 months [95% CI: 1.8, 6.5] vs 1.7 months [95% CI: 1.1, 2.1]).

For all third-line patients in this study (n = 334), the median OS was 3.4 months (95% CI: 2.9, 4.0), with only 8% surviving a year. The median OS for patients on active systemic therapy in third-line was 4.4 months (95% CI: 4.0, 5.5) with a 6- and 12-month survival rate of around 37% and 11%, respectively. Similar median estimates were noted for fourth and fifth-line; however, 1-year survival rates were < 10% (Table 4). Responders to third-line therapy had a median OS of 6.6 months (95% CI: 5.6, 8.2) and 1-year survival rate of 22% compared to a median OS of 4.0 months (95% CI: 3.1, 4.3) and 1-year survival rate of 9% for non-responders. Similarly, responders to fourth-line had higher median OS and 1-year survival rates compared to non-responders (6.3 months vs 3.2 months; 13% vs 6%). For patients receiving BSC in third-line, the prognosis was poorer, with median OS of < 1 month and 6-month survival rate of < 10%. Similar estimates were noted for fourth- and fifth-line BSC. While the median OS for BSC patients categorized as being treatment-eligible was slightly higher compared to all BSC patients (1.3 vs 0.9), the 6-month survival rates were similar. Survival curves are presented in Fig. 2.

Table 2
Treatment Patterns of SCLC Patients.

	All 3L Patients (n = 334)	All 4L Patients (n = 136)	All 5L Patients (n = 41)
First-line active systemic therapy regimen type, n (%)			
Platinum + etoposide ± other	321 (96.1)	N/A	N/A
Platinum ± other (no etoposide)	12 (3.6)		
Etoposide only	1 (0.3)		
Second-line active systemic therapy regimen type, n (%)			
Platinum + etoposide ± other	48 (14.4)	N/A	N/A
Platinum ± other (no etoposide)	64 (19.2)		
CAV only	6 (1.8)		
Topotecan only	162 (48.5)		
Irinotecan only	6 (1.8)		
Gemcitabine only	2 (0.6)		
Etoposide only	1 (0.3)		
Taxane ± other	39 (11.7)		
IO agent only	2 (0.6)		
Other chemotherapy	4 (1.2)		
Treatment status, n (%)	**Treatment status in 3L**	**Treatment status in 4L**	**Treatment status in 5L**
BSC	85 (25.4)	63 (46.3)	16 (39.0)
Treatment-eligible BSC	47 (14.1)	33 (24.3)	9 (22.0)
Systemic Treatment	249 (74.6)	73 (53.7)	25 (61.0)
ECOG prior to line of therapy initiation, n (%)	**ECOG prior to 3L initiation**	**ECOG prior to 4L initiation**	**ECOG prior to 5L initiation**
0	17 (6.8)	6 (8.2)	2 (8.0)
1	116 (46.6)	30 (41.1)	10 (40.0)
2	35 (14.1)	15 (20.5)	3 (12.0)
3	7 (2.8)	3 (4.1)	0
Unknown	74 (29.7)	19 (26.0)	10 (40.0)
	3L active systemic treatment (n = 249)	**4L active systemic treatment (n = 73)**	**5L active systemic treatment (n = 25)**
Active Systemic Treatment Characteristics			
Duration of treatment, months			
Mean (SD)	2.1 (2.0)	1.7 (2.0)	1.9 (1.5)
Median	1.5	1.3	1.5
Treatment-free interval, months			
Mean (SD)	0.8 (0.8)	1.3 (1.9)	1.2 (1.4)
Median	0.6	0.5	0.9
Active systemic therapy regimen type, n (%)			
Platinum + etoposide ± other	19 (7.6)	3 (4.1)	0 (0.0)
Platinum ± other (no etoposide)	37 (14.9)	19 (26.0)	7 (28.0)
CAV only	18 (7.2)	3 (4.1)	3 (12.0)
Topotecan only	60 (24.1)	7 (9.6)	0 (0.0)
Irinotecan only	14 (5.6)	2 (2.7)	2 (8.0)
Gemcitabine only	9 (3.6)	7 (9.6)	2 (8.0)
Etoposide only	4 (1.6)	1 (1.4)	1 (4.0)
Taxane ± other	71 (28.5)	15 (20.5)	5 (20.0)
IO agent only	9 (3.6)	7 (9.6)	1 (4.0)
Other chemotherapy	8 (3.2)	9 (12.3)	4 (16.0)

Key: 3L – third-line; 4L – fourth-line; 5L – fifth-line; BSC – best supportive care; CAV – cyclophosphamide + Adriamycin + vincristine; CI – confidence interval; ECOG – Eastern Cooperative Oncology Group; IO – immuno-oncology; N/A – not applicable; SCLC – small cell lung cancer; SD – standard deviation.

4. Discussion

To our knowledge, this study represents the largest and first US-based retrospective evaluation of treatment patterns and outcomes of SCLC patients receiving active systemic therapy or BSC in the third-line plus setting. Unconfirmed physician-assessed response to active systemic therapy in third-line SCLC was modest, with only 21% being deemed to have responded to therapy and having a mean DoR of < 3 months. Progression was reported in over 90% of patients receiving third-line systemic therapy, with median PFS of approximately 2 months. The median OS in patients initiating active systemic therapy in third-line was relatively poor, with a 6- and 12-month survival rate of 37% and 11%, respectively, and a median OS of < 4.5 months. For patients receiving BSC in third-line, the prognosis was poorer, with a median OS of < 1 month and a 6-month survival rate < 10%.

The response rate to third-line therapy in this large retrospective US-based cohort analysis is similar to what has been reported in smaller retrospective analyses published to date. The response rate in previous small single-center retrospective analyses and single-arm trials has been reported to range from 14% to 31% in patients receiving third-line therapy [18–21]. In a multicenter analysis including 120 patients receiving third-line chemotherapy for SCLC, the response rate was reported at 18% [22]. Importantly, no CRs were reported beyond third-line in this analysis. The response rate in our analysis remained comparable among third- and fourth-line therapy and decreased in patients receiving fifth-line therapy; this differs slightly from what has been reported previously, with decreasing response rates with each subsequent line of therapy [18]. In a retrospective, single-center analysis of SCLC patients receiving first-line therapy or later, the ORR was 14% in third-line, 8% in fourth-line, and 0% in fifth-line [18].

Among patients receiving third-line systemic therapy, both the median PFS (2.3 months) and median OS (4.4 months) were poor, echoing what has been published previously in smaller analyses [19–22]. Consistent with these findings, one of the larger multicenter

Table 3
Physician-assessed ORR and DoR[a] for Active Systemic Therapy.

	3L (n = 249)	4L (n = 73)	5L (n = 25)
ORR, n (%; 95% CI)	53 (21.3; 16.4, 26.9)	16 (21.9; 13.1, 33.1)	3 (12.0; 2.6, 31.2)
CR	1	0	0
PR	52 (20.9; 16.0, 26.5)	16 (21.9; 13.1, 33.1)	3 (12.0; 2.6, 31.2)
DoR (months), median (95% CI)	2.6 (1.9, 3.1)	2.0 (0.9, 2.2)	N/A[b]

Key: 3L – third-line; 4L – fourth-line; 5L – fifth-line; CI – confidence interval; CR – complete response; DoR – duration of response; ORR – overall response rate; N/A – not applicable; PR – partial response; SCLC – small cell lung cancer.
[a] For those who responded.
[b] Data not available due to small sample size.

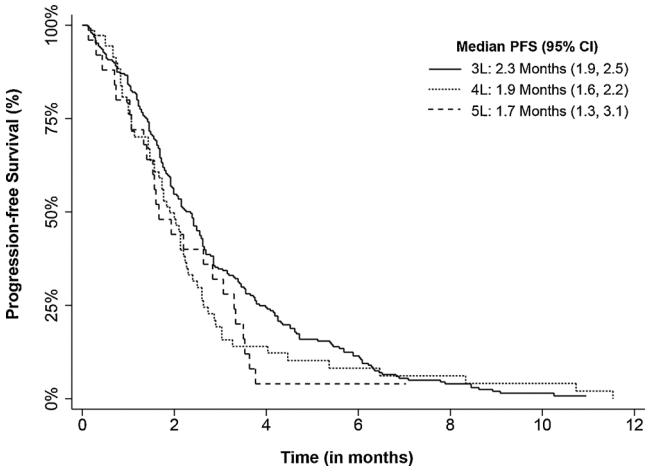

Fig. 1. Kaplan-Meier Curves for Progression-free Survival by Line of Therapy.
KEY: 3L – third-line; 4L – fourth-line; 5L – fifth-line; CI – confidence interval; PFS – progression-free survival.

Table 4
OS for Active Systemic Therapy and/or BSC by Line of Therapy Setting.

	3L	4L	5L
Active systemic therapy	N = 249	N = 73	N = 25
Died, n (%)	204 (81.9)	59 (80.8)	23 (92.0)
Median (95% CI), months	4.4 (4.0, 5.5)	4.1 (2.8, 5.3)	4.7 (2.3, 5.7)
OS rate, %			
6 months	36.6	35.9	30.0
12 months	11.4	7.8	5.1
BSC (all)	N = 85	N = 63	N = 16
Died, n (%)	78 (91.8)	58 (92.1)	16 (100.0)
Median (95% CI), months	0.9 (0.6, 1.2)	1.1 (0.9, 1.9)	1.1 (0.5, 2.6)
OS rate, %			
6 months	8.8	5.3	0.0
BSC (treatment-eligible)	N = 47	N = 33	N = 9
Died, n (%)	45 (95.7)	30 (90.9)	9 (100.0)
Median (95% CI), months	1.3 (1.0, 1.5)	1.7 (1.0, 2.6)	2.3 (0.8, 3.1)
OS rate, %			
6 months	8.8	10.1	0.0
Active systemic therapy + BSC (all)	N = 334	N = 136	N = 41
Died, n (%)	285 (85.3)	117 (86.0)	39 (95.1)
Median (95% CI), months	3.4 (2.9, 4.0)	2.3 (1.9, 2.8)	2.7 (1.6, 3.9)
OS rate, %			
6 months	32.1	21.3	18.1
12 months	8.1	4.1	3.1
Active systemic therapy + BSC (treatment-eligible)	N = 296	N = 106	N = 34
Died, n (%)	252 (85.1)	89 (84.0)	32 (94.1)
Median (95% CI), months	3.8 (3.4, 4.5)	3.0 (2.3, 4.1)	3.3 (2.2, 4.9)
OS rate, %			
6 months	35.1	27.6	22.0
12 months	8.6	5.2	0.0

Key: 3L – third-line; 4L – fourth-line; 5L – fifth-line; BSC – best supportive care; CI – confidence interval; OS – overall survival.

international analyses conducted among 120 patients found the median PFS and OS from the start of third-line therapy to be 2.0 months and 4.7 months, respectively [22]. The Simos et al. analysis included a platinum-sensitive patient population, with 90% of patients achieving a CR or PR with their first-line therapy; further, all third-line responders responded to platinum-based therapy in the front line [22]. Together, these analyses independently confirm the poor outlook for third-line SCLC patients, where for the subpopulation of patients able to receive third-line treatment, just over a third of patients survive for 6 months and only 11% to 12% survive for 1 year. One important distinction of the studies that have assessed patients receiving therapy in the third-line-plus setting is the assessment of response rates and progression. For example, in our analysis, both response rates and progression were physician-assessed, not meeting the strict criteria as provided by RECIST [23]. Therefore, it is possible that ORR and PFS are slightly higher than what would be expected when using RECIST criteria. The study by Simos et al. used RECIST v1.1 criteria to assess both response to chemotherapy and progression of disease [22]. In this retrospective analysis, the ORR was 18%, slightly lower than the ORR reported in our study, and the median PFS was essentially similar (2.3 vs 2.0 months) [22].

Clinically, many patients who are eligible to receive additional active therapy choose not to because of their negative perception of the side effects of chemotherapy. For those treatment-eligible patients who receive only BSC, the prognosis is extremely poor, with < 10% of patients surviving 6 months and most dying within 6 weeks. The prognosis is even worse for those patients deemed not to be treatment-eligible in the third-line setting. To date, this is the only publication reporting outcomes of patients receiving BSC after 2 lines of therapy for SCLC. Two studies reviewing treatment of SCLC patients in the second-line setting have shown that patients receiving treatment have significantly better median survival compared with those who received BSC alone [16,24]. The first study followed 286 patients with relapsed disease after first-line chemotherapy, of whom 120 patients received second-line chemotherapy and 166 patients received BSC [24]. Patients administered second-line chemotherapy lived significantly longer, with a median OS of 5.3 months vs 2.2 months in those who received BSC only ($P < 0.001$). Additionally, topotecan was compared to BSC in the second-line setting in 141 patients with SCLC who had relapsed after first-line therapy [16]. In this study, topotecan significantly improved median OS compared with BSC by approximately 3 months (25.9 weeks vs 13.9 weeks, respectively) [16]. The results of our analysis are similar to those reported in the second-line SCLC setting in that patients who received BSC had shorter median OS compared with those who received active treatment.

Key limitations of the current study primarily relate to the retrospective nature of the data source. While the data source represents the real-world treatment patterns for patients diagnosed with and treated for SCLC, outcomes such as ORR and progression may not necessarily be defined as precisely as in a clinical trial. Specifically, in clinical trials, the RECIST v1.1 criteria are used to define ORR and progression [23]. However, in this study, the ORR and progression were physician-assessed. Thus, the criteria in making the determination of response or progression were not often documented in physician notes, but it is assumed that physicians are using RECIST or other clinical criteria in their decisions. Unlike active systemic treatment, where the start date of the regimen was used as time zero for OS computation, a clear start date for BSC was not often documented in the physician notes and was assumed to be the day after progression. While every effort was made to capture ECOG PS, this was not consistently reported in the patient charts. Thus, a proxy had to be used for defining BSC patients who were eligible for active treatment in the absence of their ECOG score, which may slightly overestimate the OS of that subset. Patients in this study were selected from a community oncology setting in the US, which may limit the generalizability of the results to patients treated in an academic setting or other international settings.

In summary, this is the largest retrospective cohort analysis to date reviewing the outcomes of SCLC patients who received third-line systemic therapy or BSC, the latter of which was further segmented based on patient eligibility for third-line systemic treatment. SCLC patients receiving active systemic treatment in third-line or later settings demonstrated modest response rates and short survival. Furthermore, patients left untreated and placed on BSC typically live < 1 month. This analysis found that a quarter of third-line SCLC patients were either not eligible for, or chose not to receive, active therapy in the third-line. Thus, for all third-line patients in this study (n = 334), the median OS was 3.4 months, with only 8% of patients surviving for at least 1 year. While prognosis and outcomes in SCLC are known to be poor in later lines of therapy, there are limited real-world estimates of PFS and OS in addition to response rates of existing therapies. The current study represents one of the largest real-world studies to date that provides this information. This information on the current standard of care in SCLC can be leveraged for informing future trial design and measurement by providing a historical landscape assessment to help assess the incremental value of newer products being evaluated for SCLC. This application of real-world evidence to future trial design aligns with the intent of Section 3022 of the 21 st Century Act [25], which focuses on the use of real-world evidence in drug development and regulatory decision making.

Funding

This work was supported by AbbVie, North Chicago, IL.

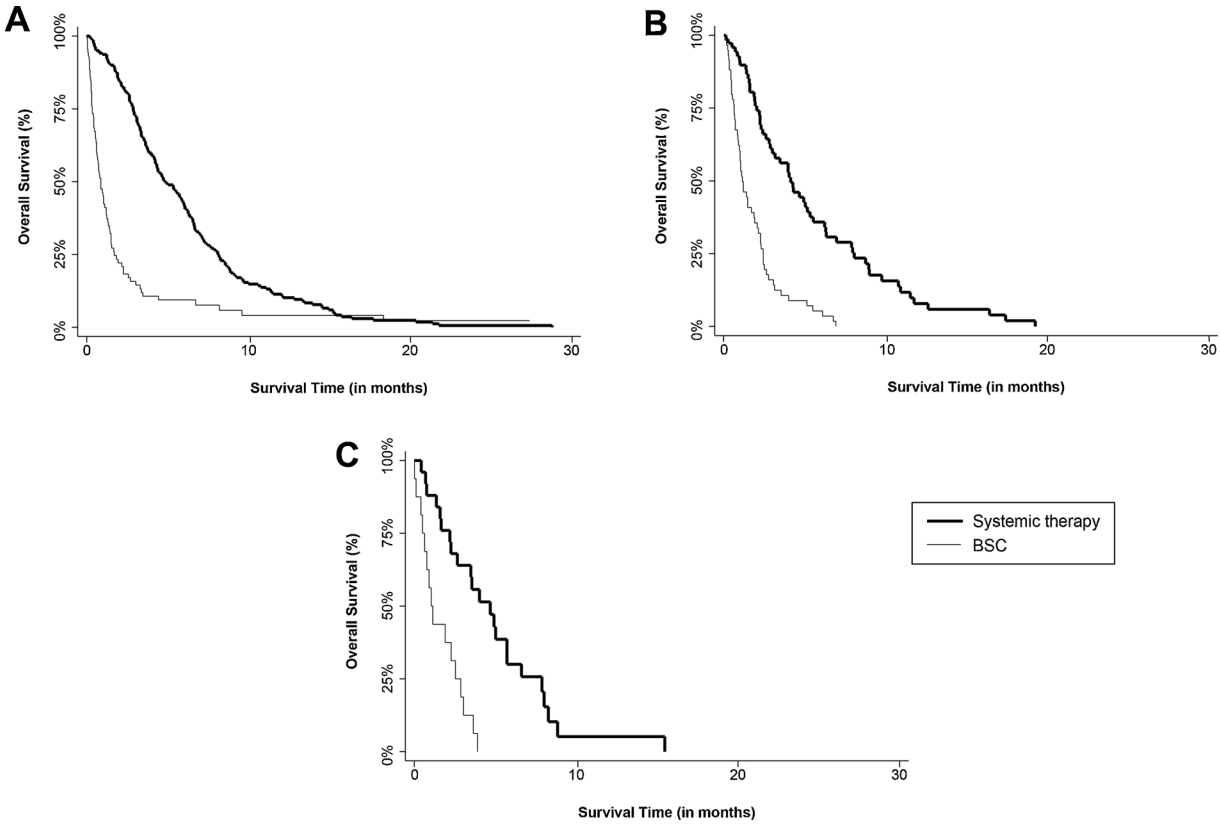

Fig. 2. Kaplan-Meier Curves for Overall Survival for Systemic Therapy and Best Supportive Care by Line of Therapy: A – 3L; B – 4L; C – 5L.
KEY: 3L – third-line therapy; 4L – fourth-line therapy; 5L – fifth-line therapy; BSC – best supportive care.

Conflict of interest statement

Manan Shah: Employee of AbbVie, may own stock or stock options in AbbVie.

AbbVie provided funding to Xcenda for conducting this work.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.lungcan.2018.11.009.

References

[1] R.L. Siegel, K.D. Miller, A. Jemal, Cancer statistics, 2018, CA Cancer J. Clin. 68 (January (1)) (2018) 7–30.
[2] Howlader N, Noone AM, Krapcho M, et al., (eds). SEER Cancer Statistics Review, 1975-2012, National Cancer Institute. Bethesda, MD. Based on November 2014 SEER data submission, posted to the SEER web site, April 2015. https://seer.cancer.gov/archive/csr/1975_2012/results_merged/sect_15_lung_bronchus.pdf. Accessed 9 April 2018.
[3] G. Metro, B. Ricciuti, R. Chiari, et al., Survival outcomes and incidence of brain recurrence in high-grade neuroendocrine carcinomas of the lung: implications for clinical practice, Lung Cancer 95 (May) (2016) 82–87.
[4] M. Zelen, Keynote address on biostatistics and data retrieval, Cancer Chemother. Rep. 4 (1973) 31–42.
[5] C.F. Mountain, Revisions in the international system for staging lung cancer, Chest 111 (June (6)) (1997) 1710–1717.
[6] F.A. Shepherd, J. Crowley, P. Van Houtte, et al., The International Association for the Study of Lung Cancer lung cancer staging project: proposals regarding the clinical staging of small cell lung cancer in the forthcoming (seventh) edition of the tumor, node, metastasis classification for lung cancer, J. Thorac. Oncol. 2 (12) (2007) 1067–1077.
[7] P. Micke, A. Faldum, T. Metz, et al., Staging small cell lung cancer: veterans Administration Lung Study Group versus International Association for the Study of Lung Cancer–what limits limited disease? Lung Cancer 37 (3) (2002) 271–276.
[8] B.E. Lally, J.J. Urbanic, A.W. Blackstock, Small cell lung cancer: have we made any progress over the last 25 years? Oncologist 12 (9) (2007) 1096–1104.
[9] National Comprehensive Cancer Network, Small Cell Lung Cancer. V2.2018. Fort Washington, PA, Accessed 16 February 2018 https://www.nccn.org/professionals/physician_gls/pdf/sclc.pdf.
[10] M. Früh, D. De Ruysscher, S. Popat, et al., Small-cell lung cancer (SCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, Ann. Oncol. 24 (October Suppl. 6) (2013) vi99-105.
[11] B.A. Chan, J.I.G. Coward, Chemotherapy advances in small cell lung cancer, J. Thorac. Dis. 5 (October (Suppl. 5)) (2013) S565–S578.
[12] D.C. Ihde, Chemotherapy of lung cancer, N. Engl. J. Med. 327 (November (20)) (1992) 1434–1441.
[13] K. Noda, Y. Nishiwaki, M. Kawahara, et al., Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer, N. Engl. J. Med. 346 (January (2)) (2002) 85–91.
[14] P.N. Lara Jr, R. Natale, J. Crowley, et al., Phase III trial of irinotecan/cisplatin compared with etoposide/cisplatin in extensive-stage small-cell lung cancer: clinical and pharmacogenomic results from SWOG S0124, J. Clin. Oncol. 27 (May (15)) (2009) 2530–2535.
[15] N. Hanna, P.A. Bunn Jr, C. Langer, et al., Randomized phase III trial comparing irinotecan/cisplatin with etoposide/cisplatin in patients with previously untreated extensive-stage disease small-cell lung cancer, J. Clin. Oncol. 24 (May (13)) (2006) 2038–2043.
[16] M.E. O'Brien, T.E. Ciuleanu, H. Tsekov, et al., Phase III trial comparing supportive care alone with supportive care with oral topotecan in patients with relapsed small-cell lung cancer, J. Clin. Oncol. 24 (34) (2006) 5441–5447.
[17] N. Asai, Y. Ohkuni, N. Kaneko, E. Yamaguchi, A. Kubo, Relapsed small cell lung cancer: treatment options and latest developments, Ther. Adv. Med. Oncol. 6 (March (2)) (2014) 69–82.
[18] M. Fiegl, A. Pircher, C. Waldthaler, et al., The TYROL Study SCLC Project: retrospective analysis of clinical features and therapeutic outcome in 484 small cell lung cancer patients diagnosed 1991–2011, Ann. Oncol. 23 (Suppl. 9) (2012) ix492–ix498 1528P.
[19] B. Lebeau, C. Chouaïd, M. Baud, M.J. Masanès, M. Febvre, Oral second- and third-line lomustine-etoposide-cyclophosphamide chemotherapy for small cell lung cancer, Lung Cancer 67 (2) (2010) 188–193.
[20] W.K. de Jong, N.H. ten Hacken, H.J. Groen, Third-line chemotherapy for small cell lung cancer, Lung Cancer 52 (3) (2006) 339–342.
[21] S. Park, M.J. Ahn, J.S. Ahn, et al., Combination chemotherapy with paclitaxel and ifosfamide as the third-line regimen in patients with heavily pretreated small cell lung cancer, Lung Cancer 58 (1) (2007) 116–122.
[22] D. Simos, G. Sajjady, M. Sergi, et al., Third-line chemotherapy in small-cell lung cancer: an international analysis, Clin. Lung Cancer 15 (2) (2014) 110–118.
[23] E.A. Eisenhauer, P. Therasse, J. Bogaerts, et al., New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1), Eur. J. Cancer 45 (January (2)) (2009) 228–247.
[24] S.1 Sundstrøm, R.M. Bremnes, S. Kaasa, et al., Second-line chemotherapy in recurrent small cell lung cancer. Results from a crossover schedule after primary treatment with cisplatin and etoposide (EP-regimen) or cyclophosphamide, epirubicin, and vincristin (CEV-regimen), Lung Cancer 48 (May (2)) (2005) 251–261.
[25] Congress.gov. H.R. 34-114th Congress: 21st Century Cures Act. https://www.congress.gov/bill/114th-congress/house-bill/34/. Accessed 5 June 2018.