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ORIGINAL ARTICLE

Treatment patterns and clinical outcomes of extensive stage small cell lung cancer (SCLC) in the real-world evidence ESME cohort before the era of immunotherapy

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Short title: Extensive stage small cell lung cancer in ESME

ABSTRACT

Background. Small cell lung cancer (SCLC) is a highly aggressive entity of lung cancer with tendency toward early recurrence after first-line treatment. As per recently updated European Society for Medical Oncology recommendations, first-line treatment with up to 4 cycles of platinum-etoposide combined with immune checkpoint inhibitor (ICIs)-targeting PD-L1, is now the standard of care. The purpose of the current analysis is to identify current patient profiles and treatment strategies in real life clinical practice, and report outcomes in Extensive Stage (ES)-SCLC.

Methods. Non-interventional, retrospective, multicenter, comparative study was carried out to describe the outcome of ES-SCLC patients included in the Epidémiologie Stratégie Médico-Economique (ESME) data platform for advanced and metastatic lung cancer. Patients were selected from 34 health care facilities between January 2015 and December 2017, before the era of immunotherapy.

Results. 1,315 patients were identified, including 64% male and 78% under 70 year-old; 24% had at least 3 metastatic sites, mainly liver metastases (43%), bone metastases (36%), brain metastases (32%). 49% received only one line of systemic treatment; 30% and 21% received 2 and 3 lines or more, respectively. Carboplatin was more frequently used than cisplatin (71% and 29%, respectively). Prophylactic cranial irradiation was infrequent (4% of patients), but 16% of patients received thoracic radiation therapy, mainly after the completion of first-line chemotherapy (72% of patients); such strategies were more frequently applied in cisplatin/etoposide than carboplatin/etoposide patients ($p=0.006$ and $p=0.015$, respectively). After a median follow-up time of 21.8 (95%CI: 20.9-23.3) months, median real-world Progression-Free Survival (rw-PFS) was 6.2 (95%CI: 5.7 ; 6.9) and 6.1 (95%CI: 5.8 ; 6.3) months for cisplatin/etoposide and carboplatin/etoposide doublet regimens, respectively; 24-

month rwPFS and Overall Survival were 3.2% (95%CI: 2.3 ; 4.2) and 22.2% (95%CI: 19.4 ; 25.1) in the whole population, respectively.

Conclusion. Our data provide with landmark reference findings on ES-SCLC before the immunotherapy era, and cover many aspects of the treatment strategy, while highlighting on the role of radiotherapy, subsequent lines of therapy, and the outcomes of patients. Generation of real-world data focusing on patients who received platinum-based chemotherapy combined with immune checkpoint inhibitors is under way.

Keywords: Small cell lung cancer; .Chemotherapy; Targeted therapy; Immunotherapy

INTRODUCTION

Small cell lung cancer (SCLC) is a highly aggressive entity of lung cancer with a rapid doubling time, and tendency toward early recurrence after first-line treatment [1]. SCLC accounts for 10-15% of all newly diagnosed lung cancer cases [1]. SCLC has mostly been classified using the Veterans Administration Lung Group (VALG) 2-stage system, which defines limited-stage and extensive-stage disease [2]: (1) limited-stage disease (LS) is defined as tumour tissue that could be encompassed in a single radiation volume, while (2) extensive-stage disease (ES) is defined as any tumour that extended beyond the boundaries of a single radiation volume. With reference to most recent guidelines, ES-SCLC is considered equivalent to metastatic disease [3]. The 5-year survival rate for ES-SCLC is estimated to be less than 5% [1, 2, 4].

As per recently updated ESMO recommendations [3], first-line treatment with up to 4 cycles of platinum-etoposide combined with immune checkpoint inhibitor (ICIs)-targeting PD-L1 [5, 6], is now standard of care. As compared with historical chemotherapy based on 6 cycles of platinum-etoposide, about 15% of patients are long-term responders [5-7], leading to a higher long-term survival rate. Second-line treatment relies on sensitivity to platinum as assessed by the delay of progression, with possible rechallenge of initial chemotherapy, or switch to second-line options [3].

Still, the reproducibility in a real-life setting of the landmark trials assessing ICIs in extensive-stage SCLC, has not been assessed so far, and may be highly dependent to the actual efficacy of platinum and etoposide chemotherapy, which has not been updated in light of recent developments in thoracic oncology, such as the better stratification of patients with systematic 18-FluoroDesoxyGlucose staging, the implementation of optimized supportive care, and the close monitoring of patients.

The purpose of the current analysis is to identify patient profiles and treatment strategies in real life clinical practice and report outcomes in ES-SCLC before the era of immunotherapy, which was made available in France in 2019; in the French context such analyses are needed to understand how novel therapies are shifting the treatment landscape and assess the actual potential improvement in patient outcomes.

MATERIAL AND METHODS

Study design

This non-interventional, retrospective, multicenter, comparative study was carried out to describe the outcome of ES-SCLC patients included in the Epidemiological Strategy and Medical Economics (ESME) data platform for advanced and metastatic lung cancer (AMLC) [8], a French national registry gathering real-life individual retrospective data from all consecutive patients ≥ 18 years diagnosed with advanced and metastatic lung cancer from 2015 at one of the 34 health care facilities (18 private non-profit Comprehensive Cancer Centers, and 16 University or General Hospitals) participating in the ESME research program in 2020. Patient-related data, hospitalization-related data and pharmacy-related data are collected, including patient demographic characteristics, pathology, treatment strategies, as well as patient outcomes.

The primary objective of the study was to describe real-world treatment pathway in patients who received first-line platinum-based and etoposide chemotherapy for ES-SCLC. Secondary objectives were to assess overall survival (OS) and progression-free survival (PFS).

Selection of patients

In this study, patient selection was based on the following criteria: 1/ histologically-confirmed SCLC, 2/ extensive stage disease by Veterans Administration Lung Group (VALG) [2], 3/ initiation of first-line treatment with platinum and etoposide, 4/ between January 2015 and December 2017, and 5/ available follow-up. Patients with prior or concomitant malignancy other than SCLC were excluded.

Regulatory aspects

In compliance with French regulations, the ESME AMLC registry was authorized by the French data protection authority (initial authorization no. DE-2017-397, and subsequent amendment dated October 14, 2019 in accordance with General Data Protection Regulation). ClinicalTrials.gov identifier is NCT 03848052. The French organization Unicancer manages the data platform according to Good Clinical, Epidemiological, and Pharmacoepidemiological Practice guidelines. Data in the registry are updated on a yearly basis and run into a data-management process. No formal dedicated informed consent is required, but all patients have approved the analysis of their electronically recorded data.

Data collection

The following data elements were collected: age; gender; Eastern Cooperative Oncology Group Performance Status (0–2 vs >2); smoking history; medical history including other cancer history, familial history of cancer; stage at primary diagnosis, histological type, number of metastatic sites, site of metastases. Treatments for SCLC were recorded including chemotherapy, radiotherapy and surgery for each treatment line. Where applicable, disease progression was collected for all treatment lines including criteria used to define progression

and date of progression. Survival status was collected. Missing data were considered as missing.

A treatment line was defined as a given therapeutic strategy delivered for ES-SCLC, until progression. The start date of the first-line therapy line was defined as the date of the first systemic treatment initiated after ES-SCLC diagnosis. Disease progression was defined as the occurrence of a new metastatic site or progression of existing metastases, regional tumoral or lymph node progression, or discontinuation of systemic treatment due to progression (assessed by the patient's physician) or death from any cause. Patients were considered resistant to first-line therapy if disease progression occurred during first-line therapy. Patients were considered refractory to first-line therapy if disease progression occurred less than 3 months after the date of last dose of first-line treatment.

Statistical analyses

Date of last follow-up was 31st December 2020. Data were summarized by median and range for continuous variables and by frequency and percentage for categorical variables. The number of missing data were presented for each variable, but not considered for the percentage calculations. Comparisons between groups were performed using the Kruskal-Wallis test for continuous variables and the Chi-squared or Fisher's exact test for categorical variables. OS was defined as the time from the start date of first-line therapy to the date of death from any cause or end of follow-up at the cut-off date. Real world PFS (rwPFS) was defined as the time from the start date of the line to the date of the first progression of the disease, or death from any cause or end of follow-up at the cut-off date. The Kaplan-Meier method was used to estimate survival end-points (OS and rwPFS). Univariate analysis was performed for each covariate of interest using a Cox regression model. Then multivariate Cox proportional hazards models were constructed using a backward step-by-step manual

selection procedure to identify time-independent prognostic factors of OS in the whole cohort and for each treatment group. Adjusted hazard ratio and associated 95% confidence interval (CI) were calculated. The final model was reached when including only significant factors at a $p < 0.05$ significance level. Adjusted survival curve were plotted according to L1 treatment strategy. Statistical analyses were performed using SAS version 9.4 or higher (SAS Institute, Inc., Cary, North Carolina, USA).

RESULTS

Patient population and characteristics

Of 21,169 patients in the ESME AMLC registry on August 2019, 2,374 had confirmed ES-SCLC, 1,315 of whom had received first-line chemotherapy with platinum and etoposide doublet regimen between January 2015 and December 2017. As shown in **Table 1**, a majority of patients were male (63.7%) and were under 70 years of age (77.7%); mean age was 63.7 years. Current or former smokers accounted for 97.9% of the population, and 15.6% had another cancer history. Co-morbidities other than cancer were frequent, as well as impaired general condition, with 30.0% of PS2 patients, and even 13% of PS3-4 patients. Overall, 24.1% had at least 3 metastatic sites, mainly liver metastases (43.1%), bone metastases (36.3%), brain metastases (31.9%), symptomatic brain metastasis 11.1%) and adrenal glands metastases (23.7%) (**Table 1**). As expected, patients who received cisplatin were younger (mean age 59.3 years) and had a better general condition (PS 0-1, 75.6%) ($p < 0.001$ and $p < 0.001$, respectively). Less than 5% of patients aged >70 years or PS3-4 received cisplatin.

Treatment strategy and disease course

In our cohort, nearly half of the patients (49.0%) received only one line of systemic treatment, because of poor general condition (11%), adverse event precluding subsequent therapies (14% of patients), or death (24% of patients) after first-line; 29.5% and 21.4% received 2 and 3 lines or more, respectively. As first-line treatment, carboplatin was more frequently used than cisplatin (70.9% and 29.1%, respectively) (**Table 1**), but median treatment duration for first-line treatment was similar in both cohorts (3.6 months). Given the study period (First treatment for lung cancer between 2015 and 2017), only 9 (0.7%) patients received

platinum/etoposide doublet chemotherapy associated with immune checkpoint inhibitor, these were excluded from the analysis population. Interestingly, prophylactic cranial irradiation was infrequent (4.0% of patients), but 16.2% of patients received thoracic radiation therapy, mainly after the completion of first-line chemotherapy (72.1% of patients) (**Table 2**); such strategies were more frequently applied in cisplatin/etoposide patients ($p=0.006$ and $p=0.015$, respectively).

Disease progression during the first-line treatment (i.e. refractory) and within the first 3 months after first-line treatment start date (i.e. resistant) was recorded in 127 and 87, 285 and 224 patients in the cisplatin- and carboplatin-based doublet regimen patients, respectively ($p=0.245$). Progression was related to occurrence of new metastatic sites in 494 (37.6%) patients, mainly brain and bone metastases (**Table 2**).

Overall, 51.0 % of the patients received a second-line treatment, mostly (95.2%) with chemotherapy. Patients who received first-line cisplatin/etoposide regimen more frequently received second-line therapy compared to those who received first-line carboplatin/etoposide (63.4% vs. 45.7%, $p<0.001$). A majority of patients treated with second-line treatment received topotecan (26.4%) – mostly in the setting of resistant or refractory disease - or carboplatine/etoposide (27.0%), carboplatine/paclitaxel (19.6%), and lurbinectedin (1.0%); adriamycin-based regimen was delivered to 10.3% of patients.

Outcomes

After a median follow-up time of 21.8 (95%CI: 20.9-23.3) months, median rwPFS was 6.2 (IC95%: 5.7 ; 6.9) and 6.1 (IC95%: 5.8 ; 6.3) months for cisplatin/etoposide and carboplatin/etoposide doublet regimens, respectively (**Table 3** and **Figure 1**). Median OS was 13.2 (IC95%: 12.2 ; 14.8) months for cisplatin/etoposide doublet regimen and 11.8 (95%IC:

11.2 ; 12.6) months for carboplatin/etoposide doublet regimen (**Table 3** and **Figure 1**); overall, median OS was 12.4 (95%IC: 11.7; 13.0) months. On the multivariate analysis, predictors of reduced OS were the following (**Table 4**): carboplatin/etoposide vs. cisplatin/etoposide doublet regimen (HR 1.60, IC95%: 1.223; 2.173, p <0.001), age >75 years vs. ≤60 years (HR 1.670, IC95% 1.309 ; 2.131, p <0.001), PS 3-4 – but not PS2- vs. PS0 (HR 2.250, IC95% 1.419 ; 3.567, p<0.001), as well as presence of bone or liver metastases at baseline (HR 1.372, IC95% 1.189 ; 1.583, and HR 1.714, IC95% 1.487 ; 1.975, p<0.001). Ultimately, 24-month rwPFS and OS were 3.2% (95%CI: 2.3 ; 4;2) and 22.2% (95%CI: 19.4 ; 25.1) in the whole population, respectively.

DISCUSSION

In this study, we aimed to describe the demographic and clinical characteristics, treatment patterns and outcomes of ES-SCLC patients mainly before the immune checkpoints inhibitors era. Our results indicate 1/ the high rate of elderly and poor general condition patients, patients with co-morbidities and or brain metastases at baseline, leading to preferentially administer carboplatin/etoposide doublet regimen, with ultimately only one line of systemic treatment for half of the patients; 2/ a significant proportion of patients receiving thoracic radiotherapy after first-line treatment in the setting of ES-SCLC; and 3/ despite resistant/refractory tumor in a majority of patients, poor median rwPFS, and limited access to subsequent lines of therapies, median OS higher than reported in recent registration clinical trials, with significant, independent, favorable impact of cisplatin-based first-line regimen.

In our study, 23% of patients were >70-year-old, 57% had co-morbidities, and 43% were PS \geq 2; brain metastases were observed in as many as 32% of patients. These factors are recognized as being associated with poor survival, as shown in our analysis, as well as in other, smaller, real-world evidence studies [9-11]. This highlights the aggressiveness of the disease, that occur in patient with a poor medical condition. While the robustness of these data to reflect the actual characteristics of patients with ES-SCLC relies on the enrolment of consecutive patients in many hospitals with various healthcare organizations and networks, - our cohort is one of the largest reported in the real-world evidence setting - our study may even underestimate those points, as only patients who received treatment are analysed. Meanwhile, one key feature of SCLC in the clinic is the rapid response to treatment, leading not to restrict access to chemotherapy based on patient PS [3].

Interestingly, in our cohort, multivariate analysis of prognostic factors, integrating confounding variables, such as age, PS, and presence of brain metastases, indicates that patients who are receiving cisplatin/etoposide vs. carboplatin/etoposide, have a better OS. While the landmark meta-analysis of historical clinical trials that compared first-line cisplatin and carboplatin did not reveal any difference in outcome [6, 7], such finding is of interest as current strategies that include immune checkpoint inhibitors have been based on carboplatin for a majority of patients [5-7]; cisplatin-etoposide was used only in the CASPIAN trial assessing durvalumab, but sub-group analyses did not reveal significant PFS or OS differences in the carbo- vs. cisplatin groups [6, 7]. Given the retrospective nature of our study, the choice of carboplatin, as per clinical practice and recommendations [3], the choice of carboplatin vs. cisplatin was related to higher age and rate of co-morbidities, poor PS, and possibly presence of symptomatic brain metastases – to avoid hyperhydration. While not enrolled in clinical trials dedicated to SCLC [5-7], these patient population may still have a benefit of immune checkpoint inhibitors, as demonstrated in metastatic NSCLC; in the

CheckMate-817 trial [12], first-line nivolumab plus ipilimumab showed a consistent safety profile in special populations, including those with ECOG PS 2 [13].

In our study, a key finding is that a high proportion of patients - 16.2% - received thoracic radiotherapy after completion of first-line treatment in the setting of ES-SCLC. Local-ablative therapies for oligoresidual disease has been extensively described in NSCLC treated with immune checkpoint inhibitors or targeted agents, with potential impact on patient outcome [14].

Such strategy has also been formally tested in ES-SCLC through the randomized, phase III CREST trial [15], that demonstrated a 2-year overall survival of 13% vs. 3% ($p=0.004$) in patients who received thoracic radiotherapy after first-line chemotherapy and prophylactic cranial irradiation; efficacy was higher in patients with less than 3 metastatic sites. Thoracic radiotherapy, as well as prophylactic brain radiotherapy, is considered optional in the most recent current guidelines for the treatment of ES-SCLC, for patients not receiving immune checkpoint inhibitors [3, 16]; indeed, thoracic radiotherapy was not part of landmark clinical trials with immunotherapy, as sequencing with maintenance remains complex.

Still, delivery of thoracic radiotherapy was not a prognostic factor on survival outcomes in our cohort; prophylactic cranial irradiation was also infrequent. In the context of combination of chemotherapy with immune checkpoint inhibitors, the role of thoracic radiotherapy has to be further assessed, as salvage therapy for refractory disease, or earlier, possibly between induction and maintenance treatment.

Ultimately, our results indicate a median rwPFS of 6.1 and 6.2 months, and a median OS of 13.2 and 11.8 months for cisplatin and carboplatin/ etoposide doublet regimens, respectively.

These OS – not rwPFS - figures are higher than that reported in the control arm of the recent landmark chemotherapy plus immunotherapy trials, ranging between 10.3 and 10.5 months, despite a selection of patients with a PS of 0 or 1, no symptomatic brain metastases, and limited co-morbidities [5-7]. Such finding is also reported in a few real-world evidence studies [9-11], and may be explained by the access, still limited to half of the patients, and the efficacy of subsequent lines of therapies, especially for the patients who received cisplatin/etoposide first-line doublet regimen, these patients are also more likely to have a better general condition, and less co-morbidities. Ultimately, the impact of the choice of cisplatin on OS reflect a higher access to second-line, as in our cohort, rwPFS rates were similar whatever the platinum salt patients, and there were more patients receiving such second-line after cis vs. carboplatin-based first-line treatment. Meanwhile, we were not able to assess some of the reported biological factor that may have a prognostic significance in SCLC, such as LDH, or the Charlson index [18].

The efficacy of second-line therapies in SCLC has been considered low, whatever is the regimen used, including topotecan [18], rechallenge with platinum/etoposide doublet regimen [19], or newer options such as lurbinectedin [20]. Deciphering the molecular biology of SCLC [21], with the concurrent development of new agents, such as those targeting DLL-3 [22] is showing promise in this setting.

To conclude, our data provide with landmark reference findings on ES-SCLC before the era of immunotherapy, and cover many aspects of the treatment strategy, while highlighting on the role of radiotherapy, subsequent lines of therapy, and the outcomes of patients. Generation of real-world data focusing on patients who received platinum-based chemotherapy combined with immune checkpoint inhibitors is under way.

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AUTHOR CONTRIBUTION

(I) Conception and design: NG, MP, CC, GS, TF

(II) Administrative support: GS

(III) Provision of study materials or patients: NG, CC, MP, DD, XQ, HL, CAV

(IV) Collection and assembly of data: GS, TF

(V) Data analysis and interpretation: GS, TF, MP, NG

(VI) Manuscript writing: All authors

(VII) Final approval of manuscript: All authors

TABLES

Table 1. Patient and tumor characteristics

	All ^a (N = 1,315)	Et/Cis (N = 380)	Et/Carbo (N = 926)	p-value
PATIENT CHARACTERISTICS				
Male gender, n (%)	837 (63.7)	227 (59.7)	604 (65.2)	<0.001
Age (years) at metastatic diagnosis				<0.001
Mean (SD)	63.7 (9.2)	59.3 (7.9)	65.5 (9.1)	
> 70, n (%)	293 (22.3)	13 (3.4)	280 (30.2)	
PS at metastatic diagnosis, n (%)				<0.001
0–1	241 (57.0)	90 (75.6)	150 (49.5)	
2	127 (30.0)	24 (20.2)	103 (34.0)	
3–4	55 (13.0)	5 (4.2)	50 (16.5)	
Not available	892	261	623	
Smoking status, n (%)				0.031
Previous or current smoker	1207 (97.9)	359 (97.8)	839 (97.3)	
Not available	77	13	64	
Asbestos exposure	95 (7.2)	27 (7.1)	68 (7.3)	0.356
Cannabis exposure	15 (1.1)	7 (1.8)	7 (0.8)	0.03
Personal medical history ^b , n (%)				<0.001
High blood pressure	470 (25.9)	107 (28.2)	359 (38.8)	
COPD	242 (18.4)	54 (14.2)	186 (20.1)	
Diabetes mellitus	201 (11.1)	39 (10.3)	160 (17.3)	
Heart failure	36 (2.0)	9 (2.4)	27 (2.9)	
Kidney failure	27 (1.5)	2 (0.5)	25 (2.7)	
Inflammatory or autoimmune disease	30 (2.3)	3 (0.8)	27 (2.9)	
Other cancer history, n (%)	195 (15.6)	51 (10.6)	208 (17.8)	<0.001
Not available	66	12	52	
TUMOR CHARACTERISTICS				
Extensive-stage diagnosis, n (%)				
De novo	1181 (89.8)	364 (95.8)	809 (87.4)	<0.001
Relapsed	134 (10.2)	16 (4.2)	117 (12.6)	
Number of metastatic sites				0.495
Mean (SD)	1.9 (1.1)	1.9 (1.2)	1.9 (1.1)	
≥3, n (%)	314 (24.1)	85 (22.5)	225 (24.6)	
Nor available	13	3	10	
Metastases sites ^c , n (%)				0.110
Liver	561 (43.1)	160 (42.4)	397 (43.3)	
Bone	473 (36.3)	159 (42.2)	310 (33.8)	
Adrenal glands	309 (23.7)	86 (22.8)	220 (24.0)	
Brain	415 (31.9)	119 (31.6)	293 (32.0)	
Brain, asymptomatic	270 (20.7)	76 (20.2)	192 (21.0)	
Brain, symptomatic	145 (11.1)	43 (11.4)	101 (11.0)	
Metastatic nodes	205 (15.7)	70 (18.6)	133 (14.5)	
Contralateral lung	183 (14.1)	49 (13.0)	133 (14.5)	
Not available	13	3	10	

COPD; chronic obstructive pulmonary disease; Et/Carbo, etoposide/carboplatin doublet regimen; Et/Cis, etoposide/cisplatin doublet regimen; PS, performance status; SD, standard deviation.

^a 9 patients have received platinum/etoposide doublet regimen with immunotherapy, and were excluded

^b Multiple possible answers.

^c Multiple possible answers.

Table 2. Treatment strategy and disease evolution

	All ^a (N = 1,315)	Et/Cis (N = 380)	Et/Carbo (N = 926)	p-value
Number of treatment lines				<0.001
Median (IQR)	2 (1;2)	2 (1;3)	1 (1;2)	
1 line, n (%)	645 (49.0)	139 (36.6)	503 (54.3)	
2 lines, n (%)	388 (29.5)	117 (30.8)	268 (28.9)	
≥3 lines, n (%)	282 (21.4)	124 (32.6)	155 (16.7)	
First-line (L1) treatment				
Time (weeks) between metastatic diagnosis and L1				0.110
Median (IQR)	2.1 (1.1;3.7)	2.4 (1.4;3.7)	2.0 (1.0;3.7)	
PCI, n (%)	53 (4.0)	24 (6.3)	27 (2.9)	0.006
Thoracic radiation therapy, n (%)	213 (16.2)	77 (20.3)	136 (14.7)	0.015
Concurrent steroids at baseline, n (%)	657 (77.1)	205 (82.7)	450 (75.1)	0.015
Disease progression during or after L1, n (%)	320 (84.2)	713 (77.0)	1040 (79.1)	0.245
- Refractory, n (%)	127 (39.7)	285 (40.0)	412 (39.6)	
- Resistant, n (%)	87 (27.2)	224 (31.4)	314 (30.2)	
New metastatic site ^b , n (%)	494 (37.6)	157 (41.3)	333 (36.0)	0.495
Brain	251 (19.1)	81 (21.3)	168 (18.1)	
Bone	106 (8.1)	26 (6.8)	80 (8.6)	
Liver	87 (6.6)	27 (7.1)	59 (6.3)	
Adrenal glands	60 (4.6)	23 (6.1)	36 (3.9)	
Metastatic nodes	44(3.3)	14 (3.7)	30 (3.2)	
Second-line (L2) treatment, n (%)	670 (51.0)	241 (63.4)	423 (45.7)	<0.001
L2 with chemotherapy, n (%)	638 (48.5)	225 (59.2)	407 (44.0)	<0.001

Et/Carbo, etoposide/carboplatin doublet regimen; Et/Cis, etoposide/cisplatin doublet regimen; IQR, interquartile range, L1, first-line treatment; L2, second-line treatment; PCI, prophylactic cranial irradiation.

^a 9 patients have received platinum/etoposide doublet regimen with immunotherapy

^b Multiple possible answers for metastases location.

Table 3. Overall survival and real-world progression-free survival of first-line treatment

	N	Survival (median)	95% CI
Overall survival (months)			
All patients	1315	12.4	11.7; 13.0
First-line with Et/Cis			
Non adjusted analysis	380	14.8	13.2; 17.3
Adjusted analysis	380	13.2	12.2 ; 14.8
First-line with Et/Carbo			
Non adjusted analysis	926	11.4	10.6 ; 12.2
Adjusted analysis	926	11.8	11.2 ; 12.6
rwProgression-free survival (months)			
All patients	1315	6.1	5.9 ; 6.3
First-line with Et/Cis	380	6.2	5.7; 6.9
First-line with Et/Carbo	926	6.1	5.8; 6.3

rwPFS and OS are calculated from the start date of first-line treatment.
CI, confidence interval; Et/Carbo, etoposide/carboplatin doublet regimen; Et/Cis, etoposide/cisplatin doublet regimen;
OS, overall survival; PFS, progression-free survival

Table 4. Multivariate analysis for overall survival

Parameters	Categories	HR [95% CI]	p-value
First-line regimen	Et/Carbo vs. Et/Cis	1.630 [1.223 ; 2.173]	<0.001
Interaction L1 strategy x time		0.974 [0.953 ; 0.995]	0.014
Age at metastatic diagnosis]60-70] vs ≤60	1.115 [0.953 ; 1.304]	0.176
]70-75] vs ≤60	0.996 [0.789 ; 1.255]	0.970
	>75 vs ≤60	1.670 [1.309 ; 2.131]	<0.001
PS at metastatic diagnosis	1 vs 0	1.114 [0.778 ; 1.594]	0.557
	2 vs 0	1.701 [1.163 ; 2.488]	0.006
	3-4 vs 0	2.250 [1.419 ; 3.567]	<0.001
	Not available vs 0	0.930 [0.670 ; 1.291]	0.665
Bone metastases at L1 start date	Yes vs No	1.372 [1.189 ; 1.583]	<0.001
Liver metastases at L1 start date	Yes vs No	1.714 [1.487 ; 1.975]	<0.001
Metastatic nodes at L1 start date	Yes vs No	1.235 [1.033 ; 1.478]	0.021
Adrenal glands metastases at L1 start date	Yes vs No	1.244 [1.063 ; 1.456]	0.007
Other metastases at L1 start date	Yes vs No	1.179 [1.002 ; 1.388]	0.048

CI, confidence interval; Et/Carbo, etoposide/carboplatin doublet regimen; Et/Cis, etoposide/cisplatin doublet regimen; HR, hazard ratio; L1, first-line therapy; PS, performance status.

FIGURE CAPTION

Figure 1. Survival of patients with extensive stage small cell lung cancer

Kaplan–Meier curves for overall survival (A) and real-world progression-free survival (B) are shown according to first-line therapy: cisplatin/etoposide doublet regimen (Blue line), etoposide/carboplatin doublet regimen (Red line).

