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ORIGINAL RESEARCH

A Multi-Country Study of the Clinical Course of Extensive-Stage Small Cell Lung Cancer: A Six-Study Analysis of Real-World Treatment Patterns and Outcomes

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Purpose: Small cell lung cancer (SCLC) is a highly aggressive malignancy with poor prognosis. Studies capturing the impact of recently approved immunotherapies are limited, highlighting a knowledge gap regarding their real-world use and effectiveness.

Patients and Methods: We examined data from 29949 patients with extensive-stage (ES)-SCLC across observational studies from the United States, United Kingdom, Spain, Taiwan, South Korea, and Japan to describe the clinical course of ES-SCLC. Data sources included electronic health record databases, registries, and claims data over time periods ranging between 2013 and 2023. Patient characteristics, recent treatment patterns, and real-world overall survival (rwOS) were assessed in each country.

Results: The most common first-line (1L) treatment was platinum plus etoposide without anti-PD-L1 agents (59–89%), followed by platinum plus etoposide with anti-PD-L1 agents (9–38%). Second-line (2L) and third-line (3L) treatments varied widely across countries. Median rwOS ranged from 8.1–11.3 months following 1L initiation, 4.8–6.9 months following 2L, and 4.1–5.5 months following 3L. Patients receiving compared to those not receiving 1L anti-PD-L1 therapy showed numerically higher median rwOS following 1L initiation, with no meaningful difference in rwOS following 2L or 3L therapy.

Conclusion: In our evaluation of real-world treatment patterns and outcomes among patients with ES-SCLC from six countries, we found that rwOS in 1L, 2L and 3L was consistently poor across countries, despite differences in patient characteristics and treatment patterns. These findings may support the generalizability of clinical evidence across geographies and highlight the need for further research to optimize treatment strategies to improve patient outcomes globally.

Keywords: small cell lung cancer, survival, extensive-stage, treatment patterns

Introduction

Worldwide, lung cancer accounted for ~2.48 million new cases in 2022.[1] Small cell lung cancer (SCLC) is a highly aggressive malignancy, accounting for approximately 15% of all lung cancers, representing approximately 372,000 new SCLC cases.[2] It is characterized by rapid growth, early metastasis, and a strong association with tobacco smoking. The disease is typically classified into two stages: limited-stage (LS-SCLC) and extensive-stage (ES-SCLC).[2] At diagnosis,

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approximately 70% of cases present as ES-SCLC, while the remaining 30% present as LS-SCLC.[2,3] Despite initial responsiveness to chemotherapy and radiotherapy, the prognosis for SCLC remains poor, largely driven by the emergence of recurrent disease which is highly resistant to systemic therapy. The median overall survival (OS) is 16 to 24 months for LS-SCLC and 6 to 12 months for ES-SCLC with current forms of treatment.[4] The five-year survival rate is less than 10%.[5,6] Over the past two decades, no significant shifts in survival outcomes for SCLC have been observed, with limited advancements in therapeutic options.[7,8] Notably, programmed cell death ligand 1 (PD-L1) inhibitors added to platinum–etoposide have become the global first-line standard based on IMpower133 (atezolizumab) and CASPIAN (durvalumab), and are endorsed by major guidelines (eg, NCCN, ESMO).[9–12] The current published literature does not adequately capture the impact of recently approved immunotherapies (IO) on outcomes, highlighting a gap in current knowledge regarding their use and effectiveness in the real-world.

Understanding global variability in patient characteristics, treatment patterns, and clinical outcomes, particularly from contemporaneous time periods following recent IO approvals, may improve the efficiency and validity of global clinical trial designs and interpretability of trial results. These findings can also help to inform the extent to which clinical evidence may be transportable across different geographies and patient populations. Here we present data describing patient characteristics, current treatment patterns, and real-world OS (rwOS) in populations with ES-SCLC across multiple countries globally. We aim to explore how these findings can inform the generalizability of clinical evidence across patient populations with ES-SCLC and support global healthcare decision-making.

Materials and Methods

Study Design, Data Sources and Patient Selection

We evaluated data from six observational studies of patients with ES-SCLC. The six studies followed a harmonized protocol and statistical analysis plan. Data sources included electronic health record databases, registries, and claims data from six countries worldwide: the United States (US), the United Kingdom (UK), Spain, Taiwan, South Korea, and Japan (Table 1). The study periods within each country were 2013–2022 in both the US and UK, 2016–2022 in Spain, 2014–2019 in Taiwan, 2018–2023 in South Korea, and 2014–2023 in Japan. Detailed descriptions of the study databases, study variables, outcome measures, and data analyses for the US[13] and Japan[14] have been published previously. For the remaining countries, additional information is provided in the Supplementary Materials.

Table 1 Overview of Data Sources, Study Period, Key Inclusion and Exclusion Criteria, by Country

	US	**UK**	**Spain**	**Taiwan**	**South Korea**	**Japan**
Data source	Flatiron Health EHR	National Cancer Registration and Analysis System	Thoracic Tumor Registry	Taiwan Cancer Registry	Samsung Medical Center EHR	MDV hospital-based claims DeSC payer-based claims
Study period	2013-2022	2013-2022	2016-2022	2014-2019	2018-2023	MDV: 2015–2022 DeSC: 2014–2023
Key inclusion criteria	ICD-9 162.x or ICD-10 C34x or C39.9, histopathology consistent with SCLC, received SACT treatment	ICD-10 C34 and ICD-O-3 8041–45/3, received SACT treatment	Diagnosis of lung cancer with histopathology consistent with SCLC, received SACT treatment	ICD-9 162.x or ICD-10 C34x and ICD-O-3 8041–45/3, clinical or pathological Stage IV	ICD-10 C34 and ICD-O-3 8041/3, received SACT treatment	ICD-10 C34X and small-cell carcinoma specific disease code, received SACT treatment

(*Continued*)

Table 1 (Continued).

	US	UK	Spain	Taiwan	South Korea	Japan
Key exclusion criteria	Diagnosed with NSCLC on or before SCLC; missing stage	Diagnosed with another prior malignancy; missing stage	Lung cancer prior to SCLC; treated with investigational or off-label use of SACT	Diagnosed with another cancer within one year preceding SCLC diagnosis	NSCLC on or before SCLC; missing stage	Received any SACT between 14 and 365 days prior to SCLC diagnosis
Staging	Derived by rule-based definitions through chart abstraction at the time of initial diagnosis	NCCN classification using the AJCC TNM staging system approximated to VALG (stage IV or T3-4)	Clinician-defined	Chart abstraction at the time of initial diagnosis	Chart abstraction at the time of initial diagnosis	MDV: AJCC TNM staging system approximated to VALG (stage IIIB/C and IV) at the time of initial diagnosis DeSC: secondary malignancy ICD-10 codes within 30 days before or after SCLC diagnosis, as a proxy for stage IV/ES-SCLC

Abbreviations: AJCC, American Joint Committee on Cancer; DeSC, DeSC Healthcare Co., Ltd.; EHR, electronic health records; ICD, International Classification of Diseases; MDV, Medical Data Vision Co., Ltd; SCLC, small cell lung cancer; NSCLC, non-small cell lung cancer; SACT, systemic anti-cancer therapy; TNM, Tumor, Node, Metastasis; VALG, Veterans Administration Lung Study Group.

Briefly, the real-world data (RWD) sources in each country captured large representative patient populations, with the exception of South Korea, where data were obtained from one large tertiary care cancer hospital (Table 1). Data sources were selected based on the quality of data regarding patient disease characteristics, the reliability of capture of the systemic anti-cancer therapies (SACT), and the reliability of mortality capture, with many data sources linked to, or validated against, national death registries. In Japan, two claims-based data sources were used: MDV (Medical Data Vision Co, Ltd) and DeSC (DeSC Healthcare Co, Ltd). Both sources were used to describe patient characteristics and treatment patterns, while DeSC was additionally used to estimate rwOS as mortality data was not well captured in MDV. Because these databases do not share patient-level identifiers, deduplication was not possible; however, analyses were conducted separately for each dataset. In the UK, privacy conditions restricted access to certain patient-level data and suppression rules were applied to prevent inadvertent patient identification (details in Supplementary Materials). The data collection windows in each country permitted the characterization of patient populations, treatment patterns, and rwOS following approval of anti-PD-L1 therapies. However, data collection was more limited in Taiwan due to the relatively shorter data collection window from 2014 to 2019.

Patients were eligible for inclusion if they were diagnosed with SCLC using relevant ICD-9 or ICD-10 diagnosis codes and histopathologic confirmation via abstraction or ICD-O-3 histology codes specific for SCLC. In addition, all patients were required to have initiated SACT for SCLC, with the exception of patients in Taiwan (Table 1). Patients were excluded if they had been diagnosed with non-small cell lung cancer (NSCLC) or another malignancy prior to diagnosis of SCLC. Patients were also excluded from outcomes analyses if there was a record of participation in an SCLC clinical trial or treatment with an investigational study drug, except in Taiwan where the identification of patients who initiated a clinical trial drug from claims data was not possible. All patients who met these eligibility criteria within the study period were included. Data were included for patients from the date of SCLC diagnosis until the end of follow-up. Patients were followed until death, and in the absence of death, until the earlier of loss to follow-up or data cutoff date.

Study Variables and Outcome Measures

Demographic and clinical characteristics, including age, sex, and Eastern Cooperative Oncology Group (ECOG) performance status score were assessed, when available, at the time of diagnosis, unless otherwise noted. Tumor stage at initial SCLC diagnosis was assessed based on the two-stage Veterans Administration Lung Study Group (VALG) staging criteria.[15] Patients with SCLC were classified into LS or ES, depending on availability of relevant information in each database (Table 1).

Line of therapy was defined starting with first-line (1L), which is defined as the first SACT received following initial SCLC diagnosis. Second-line (2L) and third-line (3L) therapies were algorithmically derived using a validated algorithm or by oncologist determined classification. Therapies of interest were categorized into regimens by line of therapy in the following hierarchical order: platinum plus etoposide without anti-PD-L1; platinum plus etoposide plus anti-PD-L1; any other IO-containing regimens; any other platinum regimens; topotecan; lurbinectedin; taxane; cyclophosphamide, doxorubicin, and vincristine (CAV); and all other regimens. Platinum agents included carboplatin or cisplatin, and anti-PD-L1 therapy included atezolizumab or durvalumab. Other IO-containing regimens was defined as receipt of other regimens containing an anti-PD-1 agent, anti-PD-L1 (excluding atezolizumab or durvalumab) agent, or CTLA-4 inhibitors. Other platinum regimens included other platinum-containing regimens that did not include etoposide. First-line anti-PD-L1 therapy was defined as receipt of atezolizumab or durvalumab at any time during 1L (concurrent with chemotherapy with or without maintenance therapy).

Platinum sensitivity status, a strong predictor of prognosis, was defined by the length of patients' chemotherapy-free interval (CTFI), calculated as the time period from the end of last chemotherapy administration in 1L to the start of 2L, among those platinum-treated in 1L who had at least 2 lines of therapy. Patients were classified into platinum resistant/refractory and sensitive using a conventionally utilized 90-day threshold.[16] Platinum resistant/refractory and sensitive status was defined as CTFI < 90 days and CTFI ≥ 90 days, respectively.

The clinical outcome measure was rwOS, defined as the time from treatment start date within a given line of therapy to the date of death. Patients without evidence of death at the end of data cutoff were censored at the time of their last confirmed activity date in the database or the data cutoff date, whichever came first.

Statistical Analysis

Patient and disease characteristics and treatment patterns were described for all study patients separately for each country. Frequencies and proportions were presented for categorical variables, while means (standard deviation [SD]) or medians (range: minimum, maximum) were presented for continuous data. Missing data were not imputed and were included in the calculation of percentages. Treatment distributions were described by line of therapy. rwOS was estimated following the start date of each line of therapy (1L-3L), both overall and in subgroups stratified by use of 1L anti-PD-L1 therapy. Median rwOS and corresponding 95% confidence intervals (CI) were calculated using Kaplan-Meier (KM) estimates. Because we did not have access to patient level data to create the combined survival curves, KM curves were regenerated using publicly available software (WebPlotDigitizer, version 5.2).[17] Final combined graphs were generated using R software and the ggplot2 package.

Each participating study complied with applicable ethical and regulatory requirements in its respective country. In Spain, the Thoracic Tumor Registry (TTR) received institutional review board (IRB) and ethics committee approval from the Hospital Universitario Puerta de Hierro-Majadahonda (No. PI 148/15), and registry data collection was authorized by the Spanish Agency for Medicines and Medical Devices (ClinicalTrials.gov identifier NCT02941458). In the United Kingdom, analyses were conducted using de-identified, population-level data released by the National Health Service (NHS) England under Section 251 of the NHS Act 2006; therefore, additional IRB or ethics committee approval was not required. The US study was determined not to involve human subjects research as defined under 45 CFR 46.102; therefore, was exempt based on IRB review. The study in South Korea was approved by the IRB and ethics committee of the Samsung Medical Center (IRB no. SMC 2023–05-088-001), with a waiver of informed consent for de-identified data. In Japan, both MDV and DeSC studies used de-identified data and were determined by an external IRB to be exempt

from review under Japanese regulations. In Taiwan, the study protocol was reviewed by the National Taiwan University Hospital IRB, which confirmed exemption under the National Health Insurance Research Database regulations.

Results

Baseline Disease Characteristics

A total of 29949 patients with ES-SCLC were included from the six studies (Table 2). Mean age at diagnosis ranged from 64.8 to 73.9 years, with the majority being males and reporting a history of smoking. Most patients (52–89%) had an ECOG performance status of 0 or 1 at diagnosis or first-line therapy initiation. Across the 3 countries where data were available, the proportion of patients with brain metastases at diagnosis varied from 5.8% (UK) to 21.6% (South Korea) and the proportion with liver metastases at diagnosis ranged between 20.2% (UK) and 41.7% (Spain).

Treatment Characteristics by Line of Therapy (1L-3L)

Eligibility criteria required patients to have received at least one line of therapy, with the exception of Taiwan where 1414 (76%) of 1866 patients with ES-SCLC initiated 1L therapy. In total, 29497 ES-SCLC patients received at least one line of therapy (Table 3), with 10172 (34.5%) receiving 2L therapy and 3529 (12.0%) receiving 3L therapy. The highest proportions of patients receiving 2L and 3L treatment were observed in the Asian countries and the lowest proportions were observed in the UK.

Among patients who were platinum-treated in 1L and received two or more lines of therapy, approximately half of the patients in the US and Spain were platinum sensitive (CTFI $\geq$ 90 days), while a much higher proportion of patients in the UK (82.3%) and South Korea (84.2%) were platinum sensitive. In Japan, platinum sensitivity differed across the two data sources (MDV: 69.9%; DeSC: 25.4%). In the 1L setting within the study periods evaluated, platinum plus etoposide

Table 2 Baseline Demographics and Disease Characteristics for Patients with ES-SCLC, by Country

	US	UK	Spain	Taiwan	South Korea	Japan	
						MDV	DeSC
N	4308	14701	1526	1866	343	6302	903
Age (years) Mean ± SD	67.5 ± 9.0	67.1 ± 9.2	64.8 ± 8.7	69.3 ± 11.1	68.7 ± 8.4	71.3 ± 8.0	73.9 ± 6.8
Males – n (%)	2221 (51.6)	7386 (50.2)	1154 (75.6)	1676 (89.8)	316 (92.1)	5102 (81.0)	741 (82.1)
Race/ethnicity – n (%)							
Asian	30 (0.7)	–	–	–	–	–	–
Black or African American	272 (6.3)	–	–	–	–	–	–
White/Caucasian	3158 (73.3)	13,845 (94.2)	1482 (97.1)	–	–	–	–
Other	396 (9.2)	439 (3.0)	44 (2.9)	–	–	–	–
Missing	452 (10.5)	417 (2.8)	0 (0)	NR[b]	NR[b]	NR[b]	NR[b]
Smoking status – n (%)							
Yes	4221 (98.0)	–	1490 (97.6)	1411 (75.6)	272 (79.3)	4944 (78.5)	85 (9.4)
No	84 (1.9)	–	30 (2.0)	258 (13.8)	28 (8.2)	811 (12.9)	76 (8.4)
Missing/incomplete	3 (0.1)	–	6 (0.4)	197 (10.6)	43 (12.5)	547 (8.7)	742 (82.2)
ECOG status – n (%)[a]							
0	755 (17.5)	2704 (18.4)	342 (22.4)	–	96 (28.0)	–	–
1	1471 (34.1)	5695 (38.7)	837 (54.8)	–	210 (61.2)	–	–
2+	1009 (23.4)	4015 (27.3)	347 (22.7)	–	22 (6.4)	–	–
Missing	1073 (24.9)	2287 (15.6)	0 (0)	–	15 (4.4)	–	–
Metastatic at diagnosis – n (%)							
Brain or CNS	–	846 (5.8)	295 (19.3)	–	74 (21.6)	–	–
Liver	–	2966 (20.2)	636 (41.7)	–	98 (28.6)	–	–

Notes: [a]ECOG status evaluated at SCLC diagnosis (UK, Spain, South Korea) or first-line therapy initiation (US). [b]Not recorded, but all patients were likely ethnic Taiwanese, Korean, and Japanese, respectively.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ES-SCLC, extensive-stage small cell lung cancer; NR, not recorded; SD, standard deviation; UK, United Kingdom; US, United States.

Table 3 Treatment Characteristics for Patients with ES-SCLC, by Country

	US	UK	Spain	Taiwan	South Korea	Japan	
						MDV	DeSC
Patients by line of therapy							
1L - n	4308	14701	1526	1414	343	6302	903
2L - n (% of 1L)	1822 (42.3)	3220 (21.9)	589 (38.6)	644 (45.5)	202 (58.9)	3241 (51.4)	454 (50.3)
3L - n (% of 1L)	680 (15.8)	637 (4.3)	213 (14.0)	229 (16.2)	97 (28.3)	1480 (23.5)	193 (21.4)
Platinum sensitivity to 1L (CTFI ≥ 90 days) – n (%) (among evaluable)	909 (51.2)	2649 (82.3)	305 (51.9)	-	202 (84.2)	908 (69.9)	115 (25.4)
1L regimens[a] – n (%)							
Platinum + Etoposide with anti-PD-L1	1121 (26.0)	265 (1.8)	133 (8.7)	0 (0.0)	130 (37.9)	823 (13.1)	264 (29.2)
Platinum + Etoposide without anti-PD-L1	2972 (69.0)	13015 (88.5)	1338 (87.7)	1048 (74.1)	213 (62.1)	4467 (70.9)	532 (58.9)
Other IO-containing regimens	28 (0.6)	17 (0.1)	3 (0.2)	0 (0.0)	0 (0.0)	4 (0.1)	19 (2.1)
Other platinum-containing regimens	91 (2.1)	990 (6.7)	40 (2.6)	175 (12.4)	0 (0.0)	807 (12.8)	77 (8.5)
Topotecan monotherapy	0 (0.0)	29 (0.2)	0 (0.0)	10 (0.7)	0 (0.0)	12 (0.2)	2 (0.2)
Taxane monotherapy	0 (0.0)	*	0 (0.0)	0 (0.0)	0 (0.0)	9 (0.1)	1 (0.1)
CAV	0 (0.0)	84 (0.6)	5 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
All other regimens[b]	96 (2.2)	28 (0.2)	6 (0.4)	181 (12.8)	0 (0.0)	180 (2.9)	8 (0.9)
Unknown	0 (0.0)	273 (1.9)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
2L regimens[a] – n (%)							
Platinum + Etoposide with anti-PD-L1	145 (8.0)	47 (1.5)	3 (0.5)	0 (0.0)	1 (0.5)	182 (5.6)	17 (3.7)
Platinum + Etoposide without anti-PD-L1	157 (8.6)	1429 (44.4)	126 (21.4)	123 (19.1)	130 (64.4)	395 (12.2)	36 (7.9)
Other IO-containing regimens	364 (20.0)	7 (0.2)	24 (4.1)	0 (0.0)	0 (0.0)	39 (1.2)	7 (1.5)
Other platinum-containing regimens	246 (13.5)	152 (4.7)	51 (8.7)	61 (9.5)	0 (0.0)	260 (8.0)	17 (3.7)
Topotecan monotherapy	407 (22.3)	607 (18.9)	127 (21.6)	361 (56.1)	0 (0.0)	206 (6.4)	21 (4.6)
Lurbinectedin monotherapy	155 (8.5)	0 (0.0)	9 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Taxane monotherapy	159 (8.7)	*	29 (4.9)	0 (0.0)	1 (0.5)	56 (1.7)	13 (2.9)
CAV	12 (0.7)	869 (27.0)	52 (8.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
All other regimens[c]	177 (9.7)	14 (0.4)	163 (27.7)	99 (15.4)	70 (34.7)	2103 (64.9)	342 (75.3)
Unknown	0 (0.0)	95 (3.0)	5 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
3L regimens[a] – n (%)							
Platinum + Etoposide with anti-PD-L1	16 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	55 (3.7)	2 (1.0)
Platinum + Etoposide without anti-PD-L1	43 (6.3)	121 (19.0)	17 (8.0)	87 (38.0)	8 (8.2)	208 (14.1)	19 (9.8)
Other IO-containing regimens	159 (23.4)	*	4 (1.9)	0 (0.0)	0 (0.0)	6 (0.4)	3 (1.6)
Other platinum-containing regimens	77 (11.3)	*	15 (7.0)	49 (21.4)	0 (0.0)	187 (12.6)	26 (13.5)
Topotecan monotherapy	117 (17.2)	241 (37.8)	50 (23.5)	54 (23.6)	0 (0.0)	230 (15.5)	28 (14.5)
Lurbinectedin monotherapy	62 (9.1)	0 (0.0)	2 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Taxane monotherapy	101 (14.9)	9 (1.4)	57 (26.8)	0 (0.0)	65 (67.0)	29 (6.1)	11 (5.7)
CAV	5 (0.7)	224 (35.2)	20 (9.4)	0 (0.0)	9 (9.3)	0 (0.0)	0 (0.0)
All other regimens[d]	100 (14.7)	0 (0.0)	44 (20.7)	39 (17.0)	15 (15.5)	765 (51.7)	104 (53.9)
Unknown	0 (0.0)	42 (6.6)	4 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Notes: *Indicates that patients received this treatment regimen, but the result has been suppressed by the data provider. [a]Platinum agents included carboplatin or cisplatin, and anti-PD-L1 therapy included atezolizumab or durvalumab. Other immunotherapy includes all other regimens containing an anti-PD-1 agent, anti-PD-L1 (excluding atezolizumab or durvalumab) agent, or CTLA-4 inhibitors; platinum includes other platinum containing regimens that do not include etoposide; other regimens include all other regimens that do not fit into any of the other categories. [b]All other regimens category predominantly comprised of etoposide in Taiwan and amrubicin monotherapy in Japan. [c]All other regimens category predominantly comprised of irinotecan monotherapy and combination therapies in Spain, etoposide in Taiwan, irinotecan monotherapy in South Korea, and amrubicin monotherapy in Japan. [d]All other regimens category predominantly comprised of irinotecan monotherapy and gemcitabine plus paclitaxel in Spain, etoposide in Taiwan, and amrubicin and irinotecan monotherapies in Japan.

Abbreviations: 1L, first line; 2L, second line; 3L third line; CAV, cyclophosphamide, doxorubicin, and vincristine; CTFI, chemotherapy free interval; ES-SCLC, extensive-stage small cell lung cancer; IO, immunotherapy; UK, United Kingdom; US, United States.

without anti-PD-L1 agents were the most frequently used regimens across all countries (58.9–88.5%). The next most common regimens were platinum plus etoposide with an anti-PD-L1 agent (26.0% in the US, 37.9% in South Korea, and 13.1–29.2% in Japan).

Treatments varied across countries in both 2L and 3L (Table 3). The most common 2L regimens were topotecan monotherapy and other IO-containing regimens in the US, platinum plus etoposide without an anti-PD-L1 agent in the UK, platinum plus etoposide without an anti-PD-L1 agent and topotecan monotherapy in Spain, topotecan monotherapy in Taiwan, platinum plus etoposide without an anti-PD-L1 agent in South Korea, and amrubicin monotherapy in Japan.

The most common 3L regimens were IO-containing regimens in the US, topotecan monotherapy and CAV in the UK, taxane (eg, docetaxel or paclitaxel) monotherapy and topotecan monotherapy in Spain, platinum plus etoposide without an anti-PD-L1 agent in Taiwan, and taxane monotherapy in South Korea. In Japan, approximately half of the patients were treated with single-agent chemotherapeutic regimens, including amrubicin and irinotecan monotherapies.

Overall Survival by Line of Therapy (1L-3L)

Across the six studies, the median rwOS by line of therapy ranged between 8.1 months and 11.3 months following 1L initiation, between 4.8 months and 6.9 months following 2L initiation, and between 4.1 months and 5.5 months following 3L initiation (Table 4). Patients in South Korea had the highest median rwOS in 1L and 2L (11.3 months [95% CI: 9.7–12.2] and 6.9 months [95% CI: 6.3–7.9], respectively), followed by Japan (9.6 months [95% CI: 8.9–10.3] and 6.7 months [95% CI: 5.9–7.4], respectively). Lower rwOS estimates were observed in the remaining countries (8.1–8.6 months for 1L and 4.8–5.6 months for 2L). However, following 3L initiation, median rwOS was largely consistent across countries (range: 4.1–5.5 months). Despite the small variations in median rwOS in the 1L and 2L settings, the KM curves for rwOS demonstrated comparable and similarly poor survival outcomes across all countries for each line of therapy (Figure 1A–1C).

Among countries conducting subgroup analyses by 1L anti-PD-L1 treatment, median rwOS following 1L initiation was numerically higher among patients who received anti-PD-L1 therapy in 1L (8.3–11.4 months) compared with patients who did not (8.0–11.1 months). The greatest differences were observed in Spain (11.3 months [95% CI: 8.6–13.2] vs 8.5 months [95% CI: 8.2–9.0]) and the UK (10.2 months [95% CI: 8.9–11.2] vs 8.0 months [95% CI: 7.9–8.1]). There was no meaningful difference in median rwOS following 2L and 3L initiation between patients who received anti-PD-L1 therapy in 1L compared to those who did not.

Discussion

To our knowledge, our examination of data from six countries across the globe represents the largest and most contemporaneous evaluation of real-world patient characteristics, treatment patterns, and outcomes among patients with ES-SCLC. In the 1L setting, platinum plus etoposide without anti-PD-L1 agents were the most frequently used regimens across countries during the study period, with varying use of anti-PD-L1 agents observed across the countries. Much more variability in treatment patterns was seen across countries in the 2L and 3L settings. Despite variations in prognostic patient characteristics (eg, smoking status; brain and liver metastases; platinum sensitivity) and treatment patterns within the study periods evaluated, we found that rwOS was remarkably similar across countries, especially following initiation of 3L therapy. Although smoking prevalence varied slightly across countries, it was high overall, in alignment with the well-established association between tobacco exposure and SCLC.[1]

Our rwOS analyses show that patients in South Korea had the highest median rwOS for 1L therapies, followed by patients in Japan. In South Korea, this may have been partially attributed to factors including the smaller sample size, single institutional practice patterns, or patients demonstrating characteristics that may be associated with better prognosis such as a higher proportion of patients with ECOG scores of 0–1 and a higher proportion of platinum sensitive patients. Both South Korea and Japan also had a larger proportion of patients who received subsequent lines of therapy, which may have contributed to longer rwOS. Overall, the modest regional differences in rwOS likely reflect variation in patient mix, treatment practices, and data characteristics across countries.

Additionally, we observed that patients who received anti-PD-L1 therapies in 1L had higher median rwOS compared to those who did not. The greatest differences in median rwOS (~2 months) were observed in Spain and the UK, while smaller numeric differences were observed in the US, South Korea, and Japan. These findings are generally consistent with the CASPIAN[9] and IMpower133[10] trials which led to approvals of durvalumab and atezolizumab, respectively. The CASPIAN trial, evaluating durvalumab plus platinum plus etoposide versus platinum plus etoposide alone, and the

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Table 4 Real-World Overall Survival of Patients with ES-SCLC Overall and by 1L Anti-PD-L1 Treatment, by Country

	US		UK		Spain		Taiwan		South Korea		Japan[a]	
	n/N	Median rwOS, Months (95% CI)	n/N	Median rwOS, Months (95% CI)	n/N	Median rwOS, Months (95% CI)	n/N	Median rwOS, Months (95% CI)	n/N	Median rwOS, Months (95% CI)	n/N	Median rwOS, Months (95% CI)
From 1L initiation												
Overall	3684/4308	8.1 (7.9–8.2)	13875/14701	8.1 (7.9–8.2)	1059/1526	8.6 (8.2–9.0)	1327/1414	8.6 (8.3–9.1)	295/343	11.3 (9.7–12.2)	732/903	9.6 (8.9-10.3)
Among patients with 1L anti-PD-L1 therapy[b]	906/1149	8.3 (7.9–8.8)	333/412	10.2 (8.9-11.2)	53/136	11.3 (8.6–13.2)	–	–	100/130	11.4 (11.7–15.3)	190/267	10.6 (9.0-11.8)
Among patients without 1L anti-PD-L1 therapy	2778/3159	8.0 (7.8–8.2)	13542/14289	8.0 (7.9–8.1)	1005/1389	8.5 (8.2–9.0)	–	–	195/213	11.1 (10.1–13.2)	542/636	9.3 (8.3–10.3)
From 2L initiation												
Overall	1597/1822	4.8 (4.5–5.1)	3066/3220	5.6 (5.3–5.8)	445/589	5.6 (4.9–6.2)	596/644	5.0 (4.5–5.6)	182/202	6.9 (6.3–7.9)	376/454	6.7 (5.9–7.4)
Among patients with 1L anti-PD-L1 therapy[b]	334/421	5.6 (4.9–6.3)	94/106	4.7 (3.9-6.2)	17/40	5.7 (4.5-NA)	–	–	57/70	7.0 (5.4–8.9)	104/146	6.9 (5.3–8.2)
Among patients without 1L anti-PD-L1 therapy	1263/1401	4.5 (4.2–4.9)	2972/3114	5.6 (5.4–5.8)	428/549	5.6 (4.8–6.2)	–	–	125/132	6.7 (5.8–8.4)	272/308	6.7 (5.8–7.8)
From 3L initiation												
Overall	596/680	4.1 (3.7–4.6)	593/637	5.0 (4.7–5.5)	163/213	4.5 (4.0–5.1)	212/229	5.4 (4.3–6.2)	90/97	5.1 (3.9–5.8)	163/193	5.5 (4.4-6.4)
Among patients with 1L anti-PD-L1 therapy[b]	126/161	4.9 (3.4–6.0)	11/11	2.6 (2.0-NE)	4/14	4.8 (1.2-NE)	–	–	27/33	5.2 (3.8–7.5)	38/53	5.5 (4.3-7.4)
Among patients without 1L anti-PD-L1 therapy	470/519	4.0 (3.7–4.5)	582/626	5.1 (4.7–5.6)	159/199	4.5 (3.9–5.1)	–	–	63/64	5.0 (3.2–6.3)	130/140	5.5 (4.2–6.4)

Notes: [a]mortality data only available for the DeSC cohort. [b]1L anti-PD-L1 therapy was defined as receipt of atezolizumab or durvalumab at any time during 1L (concurrent with chemotherapy with or without maintenance therapy).
Abbreviations: 1L, first line; 2L, second line; 3L third line; n, number of events; N, number of patients; ES-SCLC, extensive-stage small cell lung cancer; rwOS, real-world overall survival.

IMpower133 trial, evaluating atezolizumab plus carboplatin plus etoposide versus placebo plus carboplatin plus etoposide, both demonstrated an approximate 2-month extension in survival with addition of anti-PD-L1 therapy. While our data collection periods included the post-anti-PD-L1 era in most studies, data on its use remains limited as this depends on the speed of uptake, which varies across the countries studied. The true impact of anti-PD-L1 therapy use requires further research to elucidate these preliminary real-world findings.

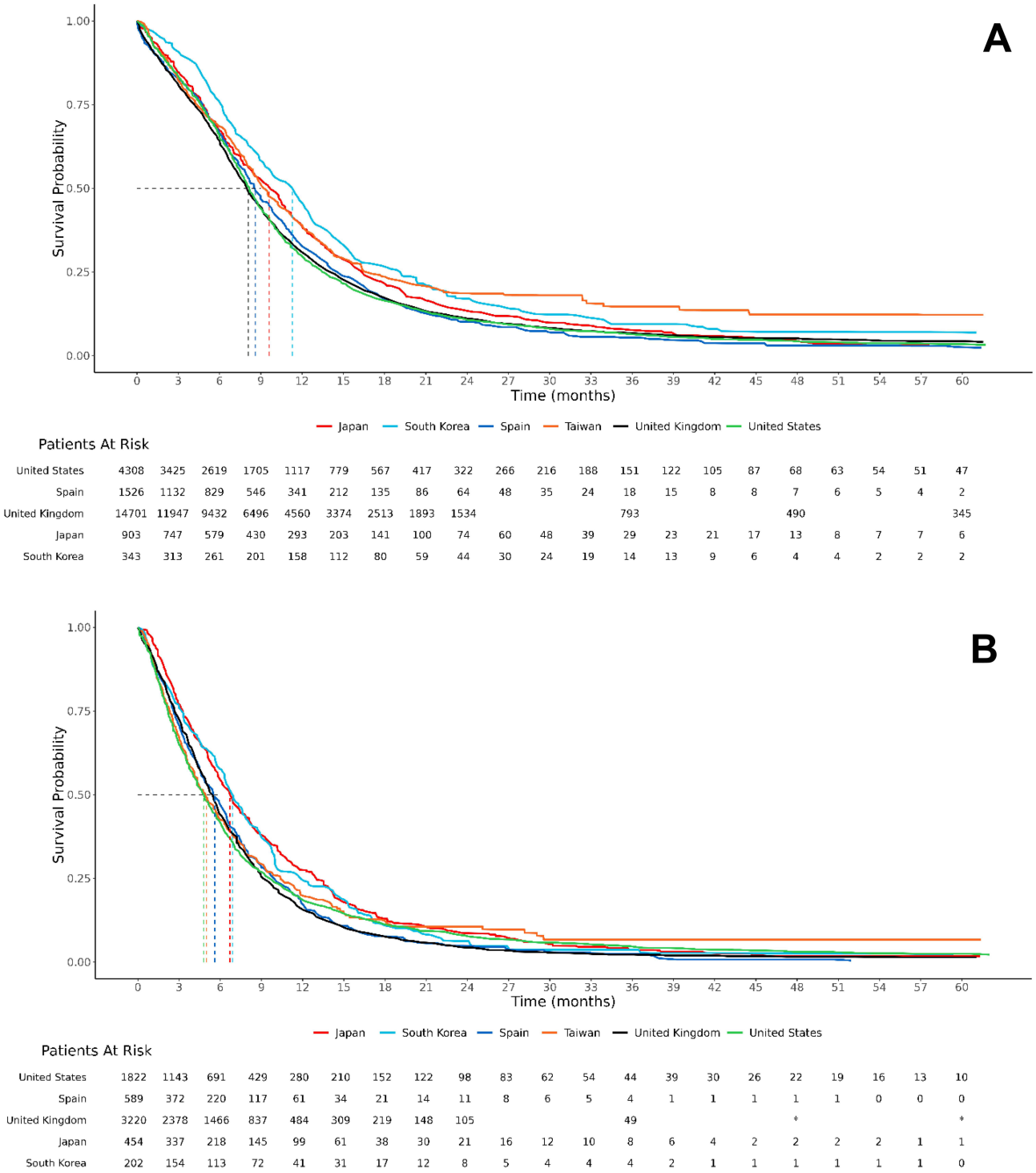

Figure 1 Continued.

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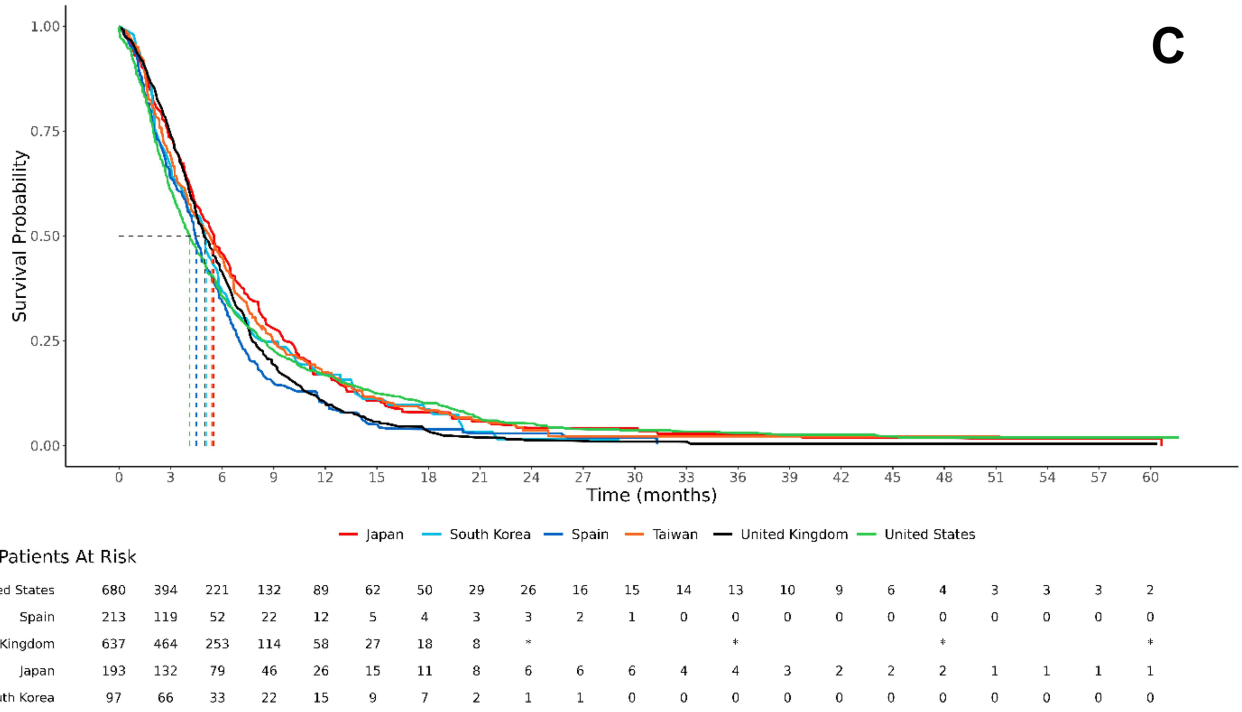

Figure 1 Real-world overall survival of patients with ES-SCLC across countries following (**A**) first-line therapy, (**B**) second-line therapy, and (**C**) third-line therapy. *indicates results suppressed by the data provider.

Notes: Number of patients at risk were not available for Taiwan due to data restrictions. For the United Kingdom, number of patients at risk were not reported at all time points. Kaplan-Meier curves from each country were regenerated using WebPlotDigitizer due to the lack of access to patient-level data necessary for creating the combined survival curves. The final combined graphs were produced using R software and include the median overall survival presented in Table 4. The median overall survival in the digitized plots may have minor variations compared to the numerical point estimates provided in Table 4.

Among 2L and 3L patients, we observed no clinically meaningful differences in median rwOS between those who received anti-PD-L1 therapy as part of a 1L regimen and those who did not. We did not evaluate rwOS by specific treatment regimens in 2L and 3L due to evolving treatment patterns and regional variations. For example, lurbinectedin is approved under accelerated approval in the United States for 2L treatment but is less commonly used outside the US, during the study period. Treatment in 2L was heterogeneous with multiple regimens being used, potentially influenced by local practice preferences. In 3L setting, treatment is also heterogenous as there is not yet an established standard of care. Overall, our findings suggest that despite differences between countries in patient characteristics and treatment patterns, rwOS for global populations of patients with ES-SCLC is similar across lines of therapy, particularly among patients who have progressed following 1L treatment (2L and 3L settings). The consistently poor prognosis across countries highlights the persisting unmet clinical needs of patients with ES-SCLC worldwide.

The consistency of rwOS outcomes across countries may also suggest that results from non-interventional studies of patients with ES-SCLC in one country could be generalizable to populations with ES-SCLC in other countries, despite potential differences in patient characteristics or treatment practices. Demonstrating consistency of important clinical outcomes across countries is a formative step in enabling a more formal future assessment of the potential transportability of study findings (ie, whether results seen in one population of patients with ES-SCLC can be applied or generalized to another population of patients with ES-SCLC). There has been an increased interest in considering real-world evidence based on populations from different countries to aid in regulatory and health technology assessment decision-making, especially when high-quality and relevant local RWD sources are limited. For example, Kent et al[18] compared patient characteristics, treatment patterns, and OS of patients with advanced NSCLC (aNSCLC) initiating 1L treatment among patients in the UK versus the US. After standardizing the US cohort to the UK cohort, the authors found that OS curves for 1L IO and targeted therapy were almost overlapping, suggesting that for aNSCLC patients receiving 1L treatment, US data could potentially be used in technology evaluations to better understand long-term OS in UK patients when UK data

are unavailable or insufficient. However, researchers who have systematically assessed the potential transportability of real-world evidence highlight the need for developing frameworks and comprehensive guidance on when such evidence might be considered transportable.[19] Importantly, when transportability can be validly demonstrated, it may be possible to inform regulatory and healthcare decisions across diverse patient groups and jurisdictions without the need to conduct new studies in countries where populations were not specifically studied.

Additionally, the ability to generalize findings from one population of patients with ES-SCLC to another may potentially have important implications for the generation of clinical evidence from oncology multi-regional clinical development programs. A recent draft FDA guidance document[20] suggests that multi-country studies can inform the design and validity of multi-country clinical trials by providing important information on the generalizability of patient characteristics and standard of care treatments across countries. For example, the higher incidence of liver metastases seen at diagnosis among patients with ES-SCLC in Spain in this study may suggest that stratification based on this parameter could be considered in future multi-country ES-SCLC clinical trials with similar eligibility criteria.

Although we harmonized protocols and statistical analysis plans across the studies conducted in each country, there remained a few differences across the studies in the availability or completeness of some data elements. For example, variability in the timeline for approval of anti-PD-L1 therapies and the speed with which these agents became accessible and reimbursable to patients varied by country, affecting the availability of these agents during the study period in each country. Minor differences across studies in the operationalization of classification to the two stage VALG staging (LS-SCLC or ES-SCLC) may have resulted in slight differences in the composition of study populations across countries. Differences in data sources, completeness, and limited follow-up for recently approved therapies across countries, limited the feasibility and validity of performing adjusted or regimen-level comparisons. However, despite these potential limitations, rwOS was remarkably similar across geographies, especially among patients following 2L and 3L treatment.

Our multi-country evaluation of rwOS among patients with ES-SCLC has several key strengths. First, the RWD sources used in each country were fit-for-purpose, employed rigorous processes in data curation, and reliably captured our mortality endpoint. Second, all but one of the data sources captured large populations representative of patients in the individual countries. Patients were drawn from community and academic centers in multiple countries with varying treatment practices, thereby enhancing the generalizability of our study findings. Third, the observational data examined reflect real-world clinical practices, offering insights that are applicable to everyday healthcare settings and capturing more diverse patients who may be poorly represented in clinical trials. The strength of the real-world evidence amassed here regarding the current standard of care and real-world treatment response may enable more efficient design of both non-interventional studies and multi-regional clinical trials. Fourth, contemporaneous data from multiple countries reflect, to the extent possible, the impact of recently approved anti-PD-L1 therapies. To our knowledge, this is the largest assessment of treatment patterns inclusive of time periods following the introduction of anti-PD-L1 agents in patients with ES-SCLC across the globe. Lastly, this description of rwOS in multiple countries and patient populations greatly enhances our understanding of the clinical course of ES-SCLC globally.

Conclusion

In our evaluation of data from six observational studies of patients with ES-SCLC from multiple countries, we found that rwOS was consistently poor across 1L, 2L, and 3L cohorts, despite differences in patient characteristics and treatment patterns. These findings may support the generalizability of clinical evidence in ES-SCLC treatment across geographies and the high unmet need underscores the pressing need for continued research to optimize treatment strategies and improve outcomes for patients with ES-SCLC worldwide.

Data Sharing Statement

The data that support the findings of the US study were originated by and are the property of Flatiron Health, Inc. Requests for data sharing by license or by permission for the specific purpose of replicating results in this manuscript can be submitted to PublicationsDataAccess@flatiron.com. The data analyzed during the UK study are available from NHS England's National Cancer Registration and Analysis Service. Restrictions apply to the access and the use of the data used to undertake the study. The data used in the Spain study were originated by and are the property of Fundacion

GECP. Requests for data sharing by permission for the specific purpose of replicating results in the study can be submitted to secretaria@gecp.org. The data sources of the Taiwan study include the Taiwan National Health Insurance Database and the Taiwan Cancer Registry. These sources are subject to specific licenses and restrictions to the study. The data can be accessed with permission from the Taiwan Health and Welfare Data Science Center (https://dep.mohw.gov.tw/DOS/cp-5119-59201-113.html). Due to legal restrictions related to the "Personal Information Protection Act," the data cannot be made publicly available. The South Korea study was reviewed and approved by the Institutional Review Board at Samsung Medical Center (SMC). IRB of SMC did not permit to share the raw data of patients without consent. The data used in the Japan study were provided by Medical Data Vision Co. Ltd. and DeSC Healthcare Co. Ltd. Due to licensing restrictions specific to the study, the data cannot be made publicly accessible.

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