ORIGINAL ARTICLE

First-Line Chemo-Immunotherapy in SCLC: Outcomes of a Binational Real-World Study

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ABSTRACT

Introduction: SCLC is characterized by aggressiveness and limited treatment options, especially in extensive-stage SCLC (ES-SCLC). Immunotherapy added to the platinum-etoposide combination has recently become standard in this setting. This retrospective study aims to evaluate the real-world effectiveness of chemo-immunotherapy in patients with ES-SCLC, focusing on subpopulations excluded from clinical trials.

Methods: A retrospective binational multicenter study was conducted, involving consecutive patients with ES-SCLC from 10 British and 10 Swiss institutions. Patients received platinum-etoposide chemotherapy in combination with immunotherapy (atezolizumab or durvalumab). Patient, tumor, and treatment details were collected. Overall survival (OS), progression-free survival, objective response rate, and safety outcomes were analyzed.

Results: A total of 436 patients were included. One hundred forty-two patients (32.6%) in our cohort would not have been eligible for the pivotal registrational trials owing to an Eastern Cooperative Oncology Group performance status of 2 or higher, autoimmune disease, active brain metastases, or steroid use. Most patients received carboplatin (96.8%) and atezolizumab (97.9%). The median progression-free survival was 5.5 months and the median OS was 9.3 months. The two-year OS was 14%. Patients with liver or bone metastases or an Eastern Cooperative Oncology Group performance status of 2 or higher had worse survival outcomes. Treatment-related adverse events were reported in 222 patients (51%) whereas immune-related adverse events occurred in 95 patients (22%). Three out of five grade 5 immune-related adverse events were caused by pneumonitis.

Conclusions: To our knowledge, this is the largest real-world cohort of patients treated with chemo-immunotherapy for ES-SCLC. Although one-third of patients would not have been eligible for pivotal trials, the survival outcomes in our cohort are similar to those in registrational trials. In particular, the number of long-term survivors and the safety data are comparable, supporting the use of chemo-immunotherapy as first-line treatment for ES-SCLC in daily clinical practice.

Keywords: SCLC; Real-world data; Immunotherapy; Special populations

Introduction

SCLC remains an aggressive disease with limited therapeutic options and is often diagnosed with the presence of advanced (extensive) disease. Traditionally, combination chemotherapy with platinum-etoposide (PE) was the standard of care for patients with extensive-stage SCLC (ES-SCLC). Although most patients initially respond to chemotherapy, the majority will experience relapse after first-line (1L) treatment, and only approximately 10% remain disease-free after two years.[1] Consolidative thoracic radiotherapy (cTRT) may reduce the risk of intrathoracic recurrence. The phase 3 CREST trial suggested that the addition of sequential cTRT to 1L chemotherapy was associated with an improvement in two-year overall survival (OS), particularly in patients with ES-SCLC with low tumor burden.[2] In 2007, a randomized clinical trial for the European Organisation for Research and Treatment of Cancer of ES-SCLC found that prophylactic cranial irradiation (PCI) reduced the risk of brain metastases and led to a small survival improvement.[3] A more recent study in Japan suggested close surveillance with magnetic resonance imaging as an alternative to PCI, with similar survival and better quality of life.[4]

First-line therapy in ES-SCLC has recently been improved with the approval of two different anti–programmed death-ligand 1 (anti–PD-L1) antibodies, atezolizumab, and durvalumab, which are used in combination with PE.

Two phase 3 clinical trials found an improvement in OS when an anti–PD-L1 antibody was added to PE and subsequently given as maintenance treatment. In the Impower 133 trial, the addition of atezolizumab to carboplatin-etoposide revealed a median OS (mOS) of 12.3 months, compared with 10.3 months in the group receiving chemotherapy alone (hazard ratio [HR] = 0.7, 95% confidence interval [CI]: 0.54–0.91, $p = 0.007$).[5] Similar findings were observed in the CASPIAN trial, where the addition of durvalumab to PE revealed improved survival outcomes, with a mOS of 12.9 months compared with 10.5 months for PE alone (HR = 0.75, 95% CI: 0.62–0.91, $p = 0.0032$).[6] Another phase 3 randomized trial, KEYNOTE-604, investigated the combination of pembrolizumab with PE in the frontline setting for SCLC. Although the trial met its co-primary end point of progression-free survival (PFS), it did not meet the other co-primary end point of OS (HR = 0.80, 95% CI: 0.64–0.98).[7] In a meta-analysis of Impower 133, CASPIAN, KEYNOTE-604, and ECOG-ACRIN EA5161, the

addition of immune checkpoint inhibitors directed against PD-1 and PD-L1 significantly improved survival by 24% among all 1553 patients (HR = 0.76; 95% CI: 0.68–0.85, $p < 0.001$).[8] Consistently across trials, the probability of being alive at 12, 18, and 24 months after treatment initiation was increased by approximately 10% with experimental versus control groups.[8] Radiotherapy (RT) may prime the immune system and enhance outcomes in combination with immune checkpoint inhibitors. The 33 trial enrolled patients with treated asymptomatic central nervous system (CNS) metastases, whereas CASPIAN also enrolled patients with untreated but asymptomatic and stable CNS metastases and revealed improved OS and PFS with durvalumab plus etoposide-platinum regardless of the presence of brain metastases. The same effect was not observed in the Impower 133 and KEYNOTE-604 trials; nevertheless, those trials did not include a substantial number of patients with CNS metastases.[9] The potential abscopal effects of RT in SCLC are still under investigation.

Despite these relevant advances in treatment, these data are not applicable to many of the patients treated in clinical practice, as they would often be excluded from clinical trials owing to the strictly limited eligibility criteria, which mainly included patients with good performance status (PS) and without relevant comorbidities.[10,11] There has been increased interest in using clinical practice data to address clinical and policy-relevant questions that cannot be answered with clinical trial data.[12,13] Recently, the first specific guidance for reporting real-world evidence studies has been published.[14] It is an effort toward providing instructions specifically for this kind of data which may not be captured adequately by the multiple complementary guidelines available. This guideline mentioned has not been used in the process of the present work as this study was done before the publication of the guidelines.

In our retrospective study, we aim to bridge the knowledge gap by assessing the effectiveness and safety profile of chemo-immunotherapy in patients with ES-SCLC treated in routine clinical practice, with particular interest on those subpopulations excluded of clinical trials but common in patients with ES-SCLC.

Materials and Methods

We performed a retrospective binational multicenter study including consecutive patients diagnosed with ES-SCLC from 10 centers in the United Kingdom (U.K.) and 10 in Switzerland (CH). Patients received at least one cycle of PE chemotherapy in combination with immunotherapy (either atezolizumab or durvalumab, as per local practice). The type and timing of all imaging procedures were performed according to local practice guidelines. Demographic, clinical, radiological, and treatment information were manually retrieved from medical records.

In Switzerland, this study was approved by the Ethics Committee of Northwestern and Central Switzerland (EKNZ 2021-01228). Only patients who have signed the general consent form, which is in use at all participating centers, and have thus given their consent to the use of disease-related data, were included. In the U.K., every hospital obtained consent from its local ethics committee. Patients in the U.K. did not sign consent forms individually as this is not requested.

OS was defined as the time from starting treatment with chemo-immunotherapy to death from any cause. PFS was defined as the time from treatment to clinical or radiological progression or death. Responses were evaluated by the investigators at the individual centers using Response Evaluation Criteria in Solid Tumors, version 1.1. Objective response rate was defined as the proportion of patients achieving complete or partial response. Adverse events (AEs) of the therapy were recorded by the treating physicians and graded on the basis of the Common Terminology Criteria for Adverse Events criteria. If the side effects were recorded and graded in the medical records, they were included in the database and used for the analysis. Patient characteristics were summarized as mean plus SD or median plus interquartile range. Chi-square tests were used to compare distributions of categorical variables between groups of interest and Mann-Whitney-Wilcoxon tests for the continuous variables. OS and PFS were estimated using the Kaplan-Meier method. No adjustment for multiple testing was performed. All statistical analyses were performed using R software.

Results

Patient and Treatment Characteristics

Between October 2018 and October 2021, 436 patients with newly diagnosed ES-SCLC who underwent chemo-immunotherapy were evaluated in 20 centers, 10 of which were in Switzerland and 10 in the U.K.

Patients included were mostly male individuals (52.3%), current or former smokers (94.5%), and the median age was 67 years old (range: 34–86 y) (Table 1). Thirty-nine patients (9%) were 75 years of age or older. The most common sites of metastatic disease at diagnosis were liver, bone, and brain, accounting for 39% (n = 170), 35% (n = 152), and 20% (n = 87), respectively. The Eastern Cooperative Oncology Group (ECOG) PS at the start of treatment was 0 to 1 in 75% (n = 329) and greater than or equal to 2 in 15% (n = 64) of the patients. For 10.6% (n = 42) ECOG data was missing. Thirty-nine

Table 1. Patients' Baseline Characteristics in Comparison to Baseline Characteristics of the Pivotal Trials Impower 133 and CASPIAN

Characteristic	CH-/UK RWD Cohort	Impower 133 (Atezolizumab-Group)	CASPIAN (Durvalumab-Group)
Number of patients	436	201	268
Gender			
Female	208 (47.7)	72 (35.8)	78 (29)
Male	228 (52.3)	129 (64.2)	190 (71)
Age, median (range)	67 (34-86)	64 (28-90)	62 (58-68)
<65 y	190 (43.6)	111 (55.2)	167 (62)
≥65 y	246 (56.4)	90 (44.8)	101 (38)
ECOG PS			
0	71 (16.3)	73 (36.3)	99 (37)
1	257 (58.9)	128 (63.7)	169 (63)
2	54 (12.4)		
3	8 (1.8)		
4	1 (0.2)		
Unknown	45 (10.3)		
Smoking history			
Current	209 (47.9)	74 (36.8)	120 (45)
Former	203 (46.6)	118 (58.7)	126 (47)
Never	10 (2.3)	9 (4.5)	22 (8)
Unknown	14 (3.2)		
Stage at initial diagnosis		NA	NA
LS-SCLC	50 (11.5)		
ES-SCLC	385 (88.3)		
Missing	1 (0.2)		
Metastases at diagnosis			
Bone	151 (34.6)	NA	NA
Liver	170 (39.0)	149 (37)	108 (40)
Brain	87 (20.0)	17 (8.5)	28 (10)

CH, Switzerland; ECOG, Eastern Cooperative Oncology Group; ES-SCLC, extensive-stage SCLC; LS-SCLC, limited-stage SCLC; NA, not applicable; PS, performance status; RWD, real-world data; UK, United Kingdom.

patients (9%) had a concomitant autoimmune disease (AID). Overall, 142 patients (32.6%) would not have been eligible for one of the pivotal trials investigating combined chemo-immunotherapy (Table 1). Fifty patients (12%) were initially diagnosed with limited-stage disease and were treated with combined radio-chemotherapy. Most patients received carboplatin (96.8%) in combination with etoposide as the chemotherapy backbone, and immunotherapy consisted of atezolizumab for most patients (97.9%) with only 2.1% receiving durvalumab. The median treatment duration was 4.4 months (range: 0–28.7 mo).

The use of PCI as part of the treatment of ES-SCLC was used more frequently in the U.K. centers (23.8% of patients) than in Switzerland (2%). Consolidative thoracic RT was given more frequently in the U.K. cohort (30.2%) than in Switzerland (10.9%).

Treatment Outcomes

Median follow-up was 16 months (range: 0–51 mo). The objective response rate was 72% with 3% and 68% of patients achieving a complete response and partial response, respectively. The median duration of response was 3.5 months (range: 3.3–4 mo). In total, 12% of patients had progressive disease as the best response.

Median PFS was 5.5 months (95% CI: 5.3–5.7), with PFS rate at one year of 14% (11%–18%) (Fig. 1). The PFS was significantly shorter in patients with ECOG PS greater than or equal to 2 (3.7 mo, 95% CI: 2.9–4.8, $p < 0.001$), liver metastases (5.2 mo, 95% CI: 4.7–5.6, $p = 0.018$) and those with bone metastases (5.2 mo, 95% CI: 4.4–5.5, $p < 0.001$) compared with the overall cohort. No differences in median PFS (mPFS) were observed for those presenting with brain metastases at diagnosis (mPFS 4.8 mo, 95% CI: 4.4–5.5, $p = 0.155$), whereas it was numerically longer in the subgroup of patients with a relapse of initially diagnosed limited-stage disease (mPFS 6.5 mo, 95% CI: 5.1–7.9, $p = 0.054$). No differences were observed regarding sex, smoking history, or participant country (U.K. and Switzerland) (Supplementary Fig. 1*A* and *B*). At progression, nearly 40% of patients received subsequent systemic anticancer therapy (46% of Swiss patients and 34.5% for the British)—with chemotherapy being the most common choice (94.8%). Of those patients receiving subsequent

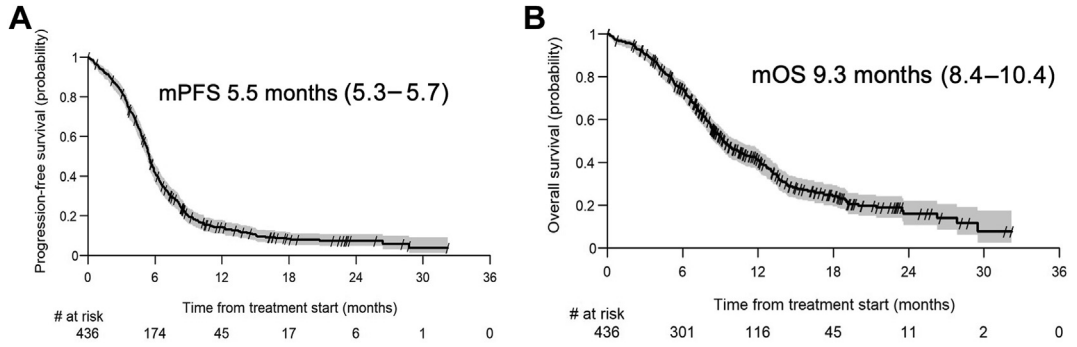

Figure 1. Progression-free survival and overall survival. Kaplan-Meier curves of the (*A*) progression-free survival and (*B*) overall survival. The width of the line shows the confidence intervals. mOS, median overall survival; mPFS, median progression-free survival.

therapy, 52% were considered platinum-sensitive and were again treated with platinum-based chemotherapy, but without the addition of immunotherapy.

The mOS was 9.3 months (95% CI: 8.4–10.4), with an OS rate at one year of 41% and 14% at 2 years (Fig. 1). In line with our data on PFS, OS outcomes were significantly worse in patients with an ECOG PS of 2 or higher (7.2 mo, 95% CI: 5–8.5, $p < 0.001$), patients with liver (7.9 mo, 95% CI: 6.9–8.6, $p = 0.001$) or bone metastases (8 mo, 95% CI: 6.7–10.1, $p = 0.003$) (Fig. 2) compared with the overall cohort. Of note, patients initially diagnosed with limited-stage disease had a significantly longer mOS (14.5 mo, 95% CI: 9.4–18.5, $p = 0.028$). Patients with brain metastases at diagnosis had similar

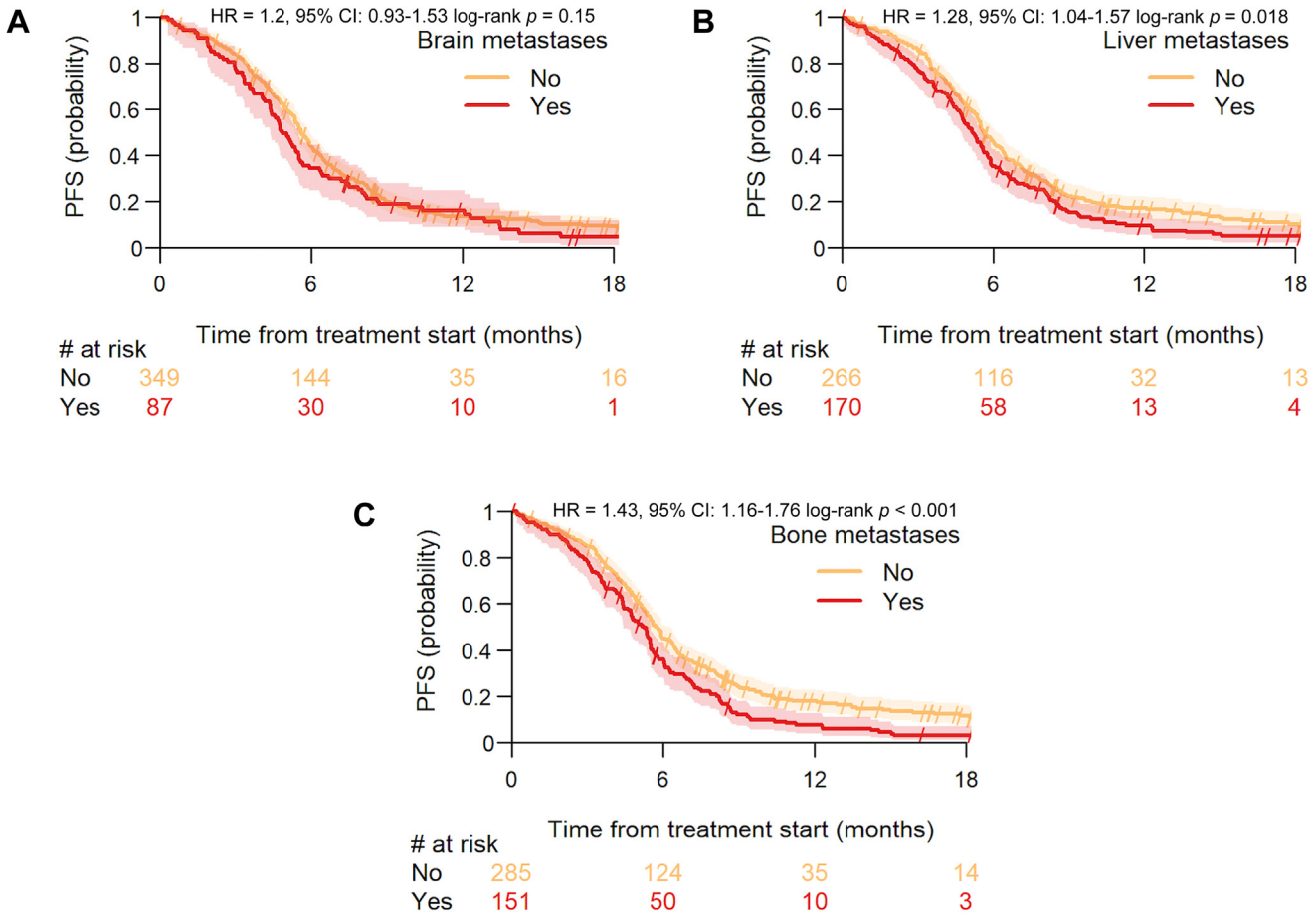

Figure 2. Progression-free survival depends on baseline characteristics. Kaplan-Meier curves of the progression-free survival depending on the presence at diagnosis of (*A*) brain metastases, (*B*) liver metastases, and (*C*) bone metastases. The width of the line shows the CIs. CI, confidence interval; HR, hazard ratio.

survival compared with their counterparts (8.6 mo; 95% CI: 6.9–10.8; $p = 0.392$). No differences in OS were observed on the basis of sex, smoking history, or participant origin (U.K. and CH).

In the cohort of patients with brain metastases at baseline, 42% (n = 15) had symptomatic brain disease, and 44% (n = 16) required steroids while on treatment with chemo-immunotherapy. Only 5% (n = 2) had received local treatment before starting systemic treatment. In this group, mPFS and mOS were 4.8 months (95% CI: 4.4–5.5) and 8.6 months (95% CI: 6.9–10.8), respectively. At progression after 1L treatment, 30.4% of the patients with available data revealed exclusive progressive intracranial disease. The subsequent line of treatment consisted of local RT (either whole-brain RT or stereotactic radiosurgery) in eight patients.

In patients who received PCI, mPFS and mOS were 7.0 months and 13.1 months, respectively. The median time to PCI from the end of chemotherapy was 44 days, and 23% (n = 13) of patients interrupted treatment with atezolizumab during RT. In the subgroup of patients who received consolidating thoracic RT, mPFS and mOS were 7.0 and 12.6 months, respectively. The use of PCI, cTRT or both was associated with significantly longer PFS (HR = 0.61, 95% CI: 0.48–0.77, $p < 0.001$) and OS (HR = 0.53, 95% CI: 0.4–0.71, $p < 0.001$) (Fig. 3).

After chemo-immunotherapy, 32% (n = 23) of patients experienced local progression, whereas progressive regional nodal disease was present in 33.8% of patients (n = 23). Notably, only a minority of patients revealed intracranial progression to chemo-immunotherapy (1.4%, n = 6).

Safety

Treatment-related AEs of any grade were reported in half of the patients (51%). Of those, 95 patients (22%) experienced an immune-related AE (irAE), and 90 (21%) patients required treatment with steroids. The incidence of G1 to 2 and G3 to 4 irAE was 62% and 22%, respectively. The most reported irAEs were: maculopapular rash (6%), hypothyroidism (3%), and pneumonitis (3%). In total, five grade 5 irAE were reported, with pneumonitis being the cause of death in three patients.

The most common non-irAEs were fatigue (13%), decreased neutrophil count (10%), anemia (9%), and decreased platelet count (8%). Febrile neutropenia was reported in 18 (4%) of patients.

In the group of patients who received consolidation thoracic RT, 38% of patients had an irAE with three episodes of grade 3 toxicity (colitis, arthritis, and myositis). Two episodes of G5 pneumonitis were reported in this population. Of note, both episodes happened less than 30 days after completing the course of RT.

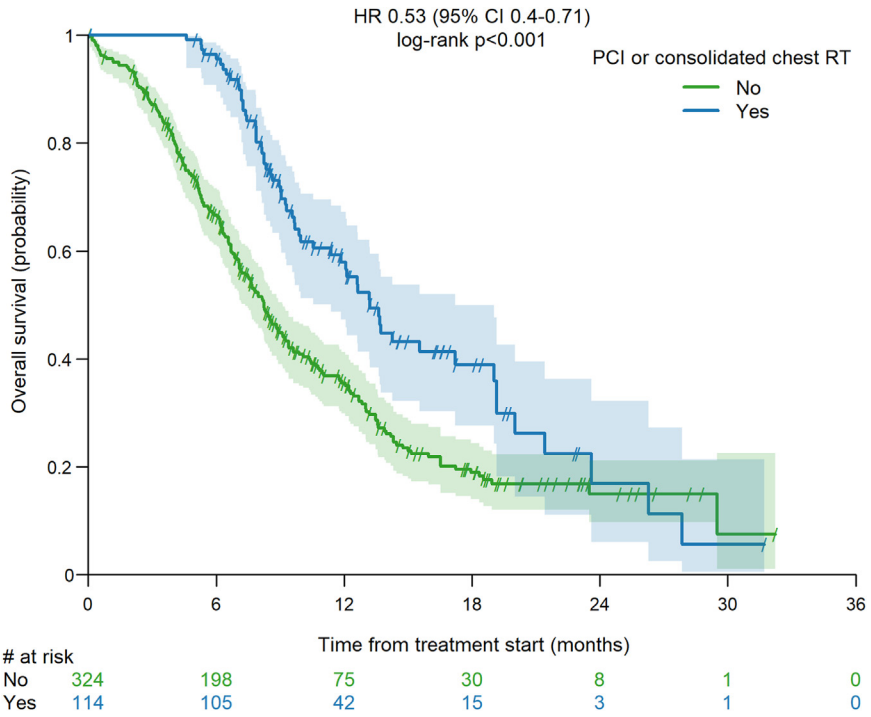

Figure 3. Overall survival depending on the use of prophylactic cranial irradiation (PCI) and/or consolidative thoracic radiotherapy (cTRT). Kaplan-Meier curves of the overall survival. The width of the line shows the confidence intervals.

Table 2. Specific Autoimmune Disorders

Autoimmune Disorders	Type (N)
Rheumatologic condition	Rheumatoid arthritis (3) Systemic lupus (1)
Endocrine condition	Type 1 diabetes mellitus (4) Hashimoto thyroiditis (3)
Gastrointestinal condition	Primary biliary cholangitis (1) Ulcerative colitis (1) Celiac disease (1)
Dermatological condition	Psoriasis (2) Vitiligo (1)
Other	Pernicious anemia (1)
Received immunosuppressive treatment	3
Last dose >2 y ago	1

Note: Type of autoimmune condition was not available in 21 patients.
N, number of patients.

Special Safety Subpopulations

Patients with AID or paraneoplastic syndromes. In total, 9% (n = 39) of the patients had an AID at baseline (Table 2). Only a minority of patients had required treatment with immunosuppressive drugs before diagnosis of SCLC, and in one case this was administered in the last two years before diagnosis. The incidence of any grade irAEs was 25.6% with five patients experiencing grade 3 toxicity. No grade 4 or 5 toxicities were reported in this subgroup of patients.

Paraneoplastic syndromes were present in 8% (n = 34) of patients at diagnosis. The specific type of syndrome was not reported for most patients but was attributed to the syndrome of inadequate antidiuretic hormone secretion in 23.5% of patients (n = 8). The incidence of any grade irAEs was 20.6% (grade reported only in two patients, with no grade 4–5 events).

Discussion

This study is, to our knowledge, the largest multicentric international data set on real-world patients with ES-SCLC treated with 1L chemo-immunotherapy.

The median PFS of patients in our cohort (5.5 mo) was the same as for patients treated in the registrational trials (5.4 mo in Impower 133, 5.1 mo in CASPIAN). Nevertheless, the mOS is slightly shorter in our real-world cohort with 9.3 months compared with 12.3 and 12.9 months in the trials. The significantly inferior mOS of patients with an ECOG PS of 2 or higher is mainly responsible for this difference. These patients were excluded from both pivotal trials, which is certainly a shortcoming, particularly in this disease entity where ECOG PS deterioration occurs rapidly owing to the often-high tumor burden in a patient population that is frequently more vulnerable owing to smoking-related comorbidities. In this regard, the relatively high proportion of patients in our cohort with an ECOG PS of 0 to 1 is surprising. These patients contribute to the "tail of the curve" observed with immunotherapy also in patients with SCLC. Notably, two-year OS is only slightly shorter in our cohort than in Impower 133 and CASPIAN (both 22%). Similar observations were reported in smaller real-world data series, underscoring the value of our study.[15–17] AEs were frequent in our cohort, although our series reported a lower incidence of treatment-related AEs than pivotal trials which may be related to the retrospective nature of this study. The incidence of grade 5 treatment-related events (1.1% in our cohort) is similar to that reported in Impower 133 (1.5%) but lower than CASPIAN (5%).[5,6] Patient characteristics and outcomes were similar among patients from the U.K. and Switzerland, with a slightly higher number of patients who received subsequent treatment in Switzerland, probably owing to differences between the populations and therapeutic options available in the respective health systems.

Patients with pre-existing AID may experience a disease flare when treated with immunotherapy and, therefore, guidelines emphasize the importance of careful consideration, weighing potential consequences against the benefits of immunotherapy in these patients.[18,19] Clinical trials typically excluded most patients with these conditions. For instance, Impower 133 excluded autoimmune conditions other than those with thyroid or skin disorders, whereas CASPIAN extended inclusion to those with coeliac disease. We observed that patients with pre-existing AID had 23% grade 3 toxicity, but no grade 4 to 5 toxicities were reported. Similarly, paraneoplastic syndromes may exacerbate after starting immunotherapy,[20] but limited data is available. Patients with these syndromes were excluded from CASPIAN if they required systemic treatment. In our series, the number of patients with a baseline paraneoplastic syndrome was small but approximately 12% of this population had equal or higher than grade 3 toxicity.

In contrast with the high prevalence of brain metastases in patients with SCLC, their presence continues to be a common exclusion criterion in clinical trials: both CASPIAN and Impower 133 excluded patients with symptomatic disease or those who required steroids. In Impower 133 any patients with untreated brain metastases were excluded. As expected, our real-world cohort shows a higher percentage of patients with brain metastases at diagnosis (20% versus 9%–14% in pivotal trials) and most patients did not receive local CNS treatment before starting chemo-immunotherapy—sometimes despite related symptoms or/and use of steroids. Prospective outcome data for this group of patients is limited, based mostly on subgroup analyses from Impower 133 and CASPIAN[21,22] where the benefit of adding immunotherapy to PE was not statistically

significant (HR: 0.01–0.96). In our cohort, outcomes were numerically slightly worse than for patients without brain metastases, but statistically significant differences were not observed.

The use of PCI as part of treatment for patients with ES-SCLC remains heterogeneous in standard clinical practice. Although its use remains fairly common in the U.K., only a small subset of Swiss patients in our cohort underwent PCI. Better survival outcomes in patients receiving PCI compared with the entire cohort were observed. Nevertheless, small numbers and selection bias preclude further conclusions. In the CASPIAN trial, where PCI was not allowed in the durvalumab arm, the numbers of patients developing brain metastases in both arms were similar (approximately 11%).[21] In the Impower 133 trial, only 22 patients received PCI in both arms. In the atezolizumab arm, the incidence of new brain lesions among those treated with PCI was less than 5% compared with 21% in those who did not receive it.[20] Ongoing clinical trials will help to elucidate the role of PCI in the era of 1L chemo-immunotherapy.[23,24]

Neither CASPIAN nor Impower 133 trials allowed cTRT, used heterogeneously in clinical practice after the CREST trial.[25] In our series, patients who received thoracic RT achieved longer mPFS and mOS. It is important to also mention the fact that there were two patients with grade 5 pneumonitis in the subgroup treated with cTRT. A recent meta-analysis including more than 1000 patients observed an increase in OS for patients with SCLC treated with chemo-immunotherapy and cTRT without an increase in grade 3 or higher toxicity.[26] Consensus has been developed to guide treatment decisions,[27] and there are ongoing clinical trials evaluating the role of cTRT in this setting.[28,29] One of these trials is the SAKK 15/19 trial investigating cTRT in combination with maintenance durvalumab after 1L chemo-immunotherapy (PE + durvalumab) in ES-SCLC.[30] Although we can reveal a significant benefit of PCI and cTRT in our analysis, these results should be interpreted with caution, as they may be affected by selection bias because particularly patients in good general condition and with a good treatment response received subsequent RT.

Our study has several limitations. The retrospective nature of the study can lead to the underrepresentation of relevant characteristics that are not well reflected in the clinical notes. This might apply in particular to irAEs because these were recorded retrospectively and the grade was not always noted by the treating physician. Nevertheless, our cohort includes data on specific patient populations (e.g., ECOG PS $\geq$ 2, previous autoimmune disorders, untreated brain metastasis at diagnosis). It is important to note that data was collected from 20 centers and two countries with different radiological follow-up protocols. Nevertheless, because of this characteristic of our data, our work also better represents the real scenarios that oncologists face every day in clinical practice.

The therapeutic landscape for ES-SCLC in the later line of therapy is changing. A wide variety of therapies and innovative combination regimens are being continuously evaluated. Potential therapeutic strategies, including aurora kinase A inhibitors, polyadenosine diphosphate-ribose polymerase inhibitors, ataxia telangiectasia, Rad3-related inhibitors, cyclin-dependent kinase 7 inhibitors, delta-like protein 3 agents, antiganglioside agents, cluster of differentiation 47 inhibitors, and lysine-specific histone demethylase 1a inhibitors, are also being examined. One of the most promising therapeutic approaches at present is antibody-drug conjugates targeting delta-like protein 3. Tarlatamab was the first substance to receive orphan drug designation from the European Medicines Agency this year, on the basis of the results of a phase 2 study in pretreated patients with ES-SCLC.[31] In this context, too, it will be important in the future to assess the efficacy and tolerability of the substances in patients in daily clinical practice from real-world analyses, who could not be included in the prospective studies owing to advanced disease associated with poor PS and comorbidities. In conclusion, our study provides real-world data on outcomes for patients with SCLC receiving 1L chemo-immunotherapy, including populations excluded from pivotal trials. Although one-third of patients in our cohort were not eligible for one of the pivotal trials, the overall outcome of patients is similar to those from registrational trials. In addition, the fact that the number of long-term survivors and safety data are comparable, our cohort confirms the use of chemo-immunotherapy in daily clinical practice. Nevertheless, it is noteworthy to mention that future trials should also consider patients usually not represented in prospective clinical trials.

CRediT Authorship Contribution Statement

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Raffaele Califano: Conceptualization, Study design, Methodology, Data acquisition, Data analysis and interpretation, Writing - original draft, Writing - review & editing, Supervision.

Sacha I. Rothschild: Conceptualization, Study design, Methodology, Data acquisition, Data analysis and interpretation, Writing - original draft, Writing - review & editing, Supervision.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at https://doi.org/10.1016/j.jtocrr.2024.100744.

References

1. Rossi A, Di Maio M, Chiodini P, et al. Carboplatin- or cisplatin-based chemotherapy in first-line treatment of small-cell lung cancer: the COCIS meta-analysis of individual patient data. *J Clin Oncol*. 2012;30:1692–1698.
2. Slotman BJ, Faivre-Finn C, van Tinteren H, et al. Which patients with ES-SCLC are most likely to benefit from more aggressive radiotherapy: a secondary analysis of the phase III CREST trial. *Lung Cancer*. 2017;108:150–153.
3. Slotman B, Faivre-Finn C, Kramer G, et al. Prophylactic cranial irradiation in extensive small-cell lung cancer. *N Engl J Med*. 2007;357:664–672.
4. Takahashi T, Yamanaka T, Seto T, et al. Prophylactic cranial irradiation versus observation in patients with extensive-disease small-cell lung cancer: a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol*. 2017;18:663–671.
5. Horn L, Mansfield AS, Szczęsna A, et al. First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. *N Engl J Med*. 2018;379:2220–2229.
6. Paz-Ares L, Dvorkin M, Chen Y, et al. Durvalumab plus platinum–etoposide versus platinum–etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. *Lancet*. 2019;394:1929–1939.
7. Rudin CM, Awad MM, Navarro A, et al. Pembrolizumab or placebo plus etoposide and platinum as first-line therapy for extensive-stage small-cell lung cancer: randomized, double-blind, phase III KEYNOTE-604 study. *J Clin Oncol*. 2020;38:2369–2379.
8. Facchinetti F, Di Maio M, Tiseo M. Adding PD-1/PD-L1 inhibitors to chemotherapy for the first-line treatment of extensive stage small cell lung cancer (SCLC): a meta-analysis of randomized trials. *Cancers (Basel)*. 2020;12:2645.
9. Melosky B, Cheema PK, Brade A, et al. Prolonging survival: the role of immune checkpoint inhibitors in the treatment of extensive-stage small cell lung cancer. *Oncologist*. 2020;25:981–992.
10. Horn L, Keedy VL, Campbell N, et al. Identifying barriers associated with enrollment of patients with lung cancer into clinical trials. *Clin Lung Cancer*. 2013;14:14–18.
11. Kawachi H, Fujimoto D, Morimoto T, et al. Clinical characteristics and prognosis of patients with advanced non-small-cell lung cancer who are ineligible for clinical trials. *Clin Lung Cancer*. 2018;19:e721–e734.
12. Sherman RE, Anderson SA, Dal Pan GJ, et al. Real-world evidence - what is it and what can it tell us? *N Engl J Med*. 2016;375:2293–2297.
13. Sanz-Garcia E, Haibe-Kains B, Siu LL. Using real-word data to evaluate the effects of broadening eligibility criteria in oncology trials. *Cancer Cell*. 2021;39:750–752.

14. Castelo-Branco L, Pellat A, Martins-Branco D, et al. ESMO Guidance for Reporting Oncology real-World evidence (GROW). *Ann Oncol*. 2023;34:1097–1112.
15. García-Campelo MR, Dómine M, de Castro Carpeño J, et al. 1995P Long-term benefit of atezolizumab plus chemotherapy in extensive stage small cell lung cancer (ES-SCLC): exploratory analysis from the IMfirst study. *Ann Oncol*. 2023;34:S1064–S1065.
16. Porte M, Vaudron A, Crequit P, et al. 2002P A multicentre study assessing the real-world effectiveness of first-line chemotherapy plus immunotherapy in extensive-stage small cell lung cancer (ES-SCLC) patients. *Ann Oncol*. 2023;34:S1068.
17. Panagiotou E, Livanou ME, Montgomery A, et al. 2007P Real-world (rw) outcomes to chemoimmunotherapy and biomarker analysis in extensive-stage small cell lung cancer (ES SCLC). *Ann Oncol*. 2023;34:S1069.
18. Abdel-Wahab N, Shah M, Lopez-Olivo MA, Suarez-Almazor ME. Use of immune checkpoint inhibitors in the treatment of patients with cancer and preexisting autoimmune disease: a systematic review. *Ann Intern Med*. 2018;168:121–130.
19. Brahmer JR, Abu-Sbeih H, Ascierto PA, et al. Society for immunotherapy of cancer (SITC) clinical practice guideline on immune checkpoint inhibitor-related adverse events. *J Immunother Cancer*. 2021;9:e002435.
20. Manson G, Maria ATJ, Poizeau F, et al. Worsening and newly diagnosed paraneoplastic syndromes following anti-PD-1 or anti-PD-L1 immunotherapies, a descriptive study. *J Immunother Cancer*. 2019;7:337.
21. Liu SV, Reck M, Mansfield AS, et al. Updated overall survival and PD-L1 subgroup analysis of patients with extensive-stage small-cell lung cancer treated with atezolizumab, carboplatin, and etoposide (IMpower133). *J Clin Oncol*. 2021;39:619–630.
22. Goldman JW, Dvorkin M, Chen Y, et al. Durvalumab, with or without tremelimumab, plus platinum–etoposide versus platinum–etoposide alone in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): updated results from a randomised, controlled, open-label, phase 3 trial. *Lancet Oncol*. 2021;22:51–65.
23. Levy A, Berghmans T, Andratschke N, et al. Prophylactic cerebral irradiation or active brain magnetic resonance imaging surveillance in small-cell lung cancer patients (EORTC-1901: PRIMALung). *J Clin Oncol*. 2023;41(16_suppl):TPS8614.
24. ClinicalTrials.gov. S1827 (MAVERICK) testing whether the use of brain scans alone instead of brain scans plus preventive brain radiation affects lifespan in patients with small cell lung cancer. https://clinicaltrials.gov/study/NCT04155034. Accessed July 12, 2024.
25. Slotman BJ, Van Tinteren H, Praag JO, et al. Use of thoracic radiotherapy for extensive stage small-cell lung cancer: a phase 3 randomised controlled trial. *Lancet*. 2015;385:36–42.
26. Feng B, Zheng Y, Zhang J, Tang M, Na F. Chemo-immunotherapy combined with consolidative thoracic radiotherapy for extensive-stage small cell lung cancer: a systematic review and meta-analysis. *Radiother Oncol*. 2024;190:110014.
27. Melosky BL, Leighl NB, Dawe D, et al. Canadian consensus recommendations on the management of extensive-stage small-cell lung cancer. *Curr Oncol*. 2023;30:6289–6315.
28. ClinicalTrials.gov. Testing the addition of radiation therapy to the usual immune therapy treatment (atezolizumab) for extensive stage small cell lung cancer, the RAPTOR trial. https://clinicaltrials.gov/study/NCT04402788. Accessed July 12, 2024.
29. ClinicalTrials.gov. Radiotherapy and durvalumab/ durvalumab combo (tremelimumab/ Olaparid) for small cell lung cancer. https://clinicaltrials.gov/study/NCT03923270. Accessed July 12, 2024.
30. ClinicalTrials.gov. Thoracic radiotherapy plus maintenance durvalumab after first line carboplatin and etoposide plus durvalumab in extensive-stage disease small cell lung cancer (ED-SCLC). https://clinicaltrials.gov/study/NCT04472949. Accessed July 12, 2024.
31. Ahn MJ, Cho BC, Felip E, et al. Tarlatamab for patients with previously treated small-cell lung cancer. *N Engl J Med*. 2023;389:2063–2075.