ORIGINAL ARTICLE

# Real-World Analysis of Clinical Characteristics and Survival Outcomes in Patients With Extensive-Stage SCLC Treated With First-Line Chemoimmunotherapy

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## ABSTRACT

**Introduction:** There are no clinically validated prognostic biomarkers in the management of extensive-stage SCLC (ES-SCLC). We explored the association between clinical characteristics and survival outcomes in patients with ES-SCLC treated with chemoimmunotherapy.

**Methods:** In this retrospective cohort study, patients with ES-SCLC treated with first-line platinum-etoposide chemotherapy and atezolizumab were identified from medical records. Pretreatment clinical characteristics, biochemical parameters, and tumor and treatment characteristics were collected. Univariate and multivariate Cox regression were used to evaluate treatment effect on progression-free survival (PFS) and overall survival (OS).

**Results:** We evaluated 75 patients in total. The median PFS and OS were 6.1 months and 9.2 months, respectively. Statistically significant associations were found with lower lactate dehydrogenase and improved OS (hazard ratio [HR] = 1.0, 95% confidence interval [CI]: 1.0–1.01, $p = 0.006$), whereas higher age (HR = 0.94, 95% CI: 0.90–0.98, $p = 0.006$) and lower neutrophil-to-lymphocyte ratio (HR = 1.08, 95% CI: 1.02–1.14, $p = 0.005$) were associated with improved PFS. The number of chemotherapy cycles received were associated with both an improved PFS (HR = 0.57, 95% CI: 0.37–0.89, $p = 0.011$) and OS (HR = 0.5, 95% CI: 0.30–0.84, $p = 0.008$).

**Conclusions:** This study highlights the important effect of chemotherapy on survival. Furthermore, the association between lactate dehydrogenase and neutrophil-to-lymphocyte ratio on survival further suggests that baseline tumor burden and optimizing sarcopenia are important factors for clinicians to consider as we seek to develop personalized treatment for this disease.

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## Introduction

Extensive-stage SCLC (ES-SCLC) is characterized by a highly aggressive disease course with rapid disease kinetics. It is almost exclusively related to smoking and harbors a poor prognosis owing to the paucity of actionable oncogenic mutation drivers, rapid tumor proliferation, and relatively limited duration of response when treated with platinum-based chemotherapy.[1] Recent advances in the treatment of ES-SCLC with the introduction of immune checkpoint inhibitors to platinum-etoposide chemotherapy have led to a modest improvement in survival and now become incorporated as the standard of care in this disease.

In the phase 3 IMpower133 study, the addition of atezolizumab, a programmed death-ligand 1 (PD-L1) antibody, to combination carboplatin and etoposide in the first-line setting resulted in a significantly longer median progression-free survival (PFS) (5.2 mo versus 4.3 mo, hazard ratio [HR] = 0.77, 95% confidence interval [CI]: 0.62–0.96, $p = 0.02$) and overall survival (OS) (12.9 mo versus 10.4 mo, HR = 0.77, 95% CI: 0.54–0.91, $p = 0.007$) compared with chemotherapy alone.[2] Importantly, at 18 months in the updated OS analysis, 13% more patients were alive in the immunotherapy plus chemotherapy arm (34%) compared with the placebo arm (21%).[3] Similarly, durvalumab, another PD-L1 antibody, was found in the phase 3 CASPIAN study to improve OS (12.9 mo versus 10.5 mo, HR = 0.73, 95% CI: 0.59–0.91, $p = 0.0047$) when combined with chemotherapy compared with chemotherapy alone.[4] A similar survival update from CASPIAN revealed that at 36 months the OS benefit was sustained with 17.6% of patients alive in the durvalumab arm compared with 5.8% in the placebo arm.[5] Both these studies have led to the establishment of anti–PD-L1 therapies in addition to platinum-etoposide chemotherapy as the current standard of care in the treatment of ES-SCLC. Despite improved outcomes with the addition of immunotherapy, the long-term prognosis of most patients remains poor as highlighted by the updated landmark survival analyses.

Several studies have evaluated whether certain biomarkers may be predictive of response. Tumor-specific characteristics such as PD-L1 expression and tumor mutational burden have not been reliably associated with immune checkpoint inhibitor benefit in ES-SCLC.[6,7] Therefore, it remains important to identify whether certain patient characteristics may have any influence on outcomes to help guide treatment. The aim of this retrospective analysis was to identify any clinical characteristics or treatment parameters associated with an improvement in PFS and OS in a real-world situation.

## Methods

### Study Population

Retrospective data from patients with ES-SCLC across two metropolitan hospitals in Melbourne, Australia, were collected. Patients with ES-SCLC aged 18 years and above who had received first-line platinum-etoposide chemotherapy with atezolizumab were identified at each participating site, and data were extracted from local medical records. Eligible patients needed to have a histologically confirmed SCLC that was radiologically confirmed to be extensive stage by either computed tomography and/or fluorodeoxyglucose-positron emission tomography imaging and have received at least one dose of chemoimmunotherapy.

### Data Collection

Data collected included patient characteristics such as age, smoking status, performance status, and body mass index (BMI); biochemical characteristics such as C-reactive protein (CRP), albumin, lactate dehydrogenase (LDH), and neutrophil-to-lymphocyte ratio (NLR); date of diagnosis, sites of metastases, treatment patterns, and date of progression and death. In this study, data were extracted and analyzed from patients diagnosed with having ES-SCLC from December 19, 2019, to October 6, 2022.

### Assessments and Statistical Analysis

Tumor assessments were performed using Response Evaluation Criteria in Solid Tumors version 1.1 retrospectively by Y.W. and J.M. OS was defined as the time from the date of commencement of treatment to the date of death or last follow-up. PFS was calculated from the date of treatment to disease progression or death. Univariate and multivariate analyses for OS and PFS were performed using Cox proportional hazards regression, with results reported as HRs and 95% CIs. Variables with $p$ less than 0.05 on univariate analysis or those deemed to be clinically relevant were entered into a hierarchical regression model to identify the independent predictors of OS and PFS. The Kaplan-Meier product-limit method was used to plot OS and PFS as a function of time. All calculated $p$ values are two sided with $p$ less than 0.05 indicating statistical significance.

Analyses were performed using the SAS software version 9.4 (SAS Institute, Cary, NC).

### Ethics Approval

Ethics approval for data collection and use of deidentified patient data was obtained from the Human Research Ethics Committee (HREC) at each participating site with a master HREC number at the primary site of HREC/85321/MonH-2002-305584(v1).

## Results

### Patient Characteristics

Between December 10, 2019, and October 6, 2022, 75 patients with ES-SCLC were identified from medical records at both cancer centers. As outlined in Table 1, most were males (51 patients, 68%), with a median age at diagnosis of 68.7 years. In addition, 73 patients (97.3%) had a smoking history. A total of 51 patients (68%) had an Eastern Cooperative Oncology Group performance status of 0 to 1, and the median BMI was 26.3. Furthermore, 54 patients (72%) had baseline CRP, and 53 patients (70.7%) had baseline albumin level available for analysis. The median follow-up period from date of diagnosis was 23.4 months. At the time of initial diagnosis, 24 (32%) had brain metastases, 62 (82.7%) had chest metastases, and 55 (73.3%) had other sites of distant metastases, including liver metastases. In addition, 15 (20%) had received palliative radiotherapy to the brain or bones for symptomatic metastases. Of the 75 patients, 61 (81.3%) completed all four cycles of chemotherapy with atezolizumab and proceeded to maintenance atezolizumab.

**Table 1.** Baseline Characteristics of Study Population

| Characteristics | All Patients |
|---|---|
| Median age (range), y | 68.7 (47-87) |
| Age group, n (%) | |
| <65 y | 42 (56) |
| >65 y | 33 (44) |
| Male sex, n (%) | 51 (68) |
| ECOG performance status score, n (%) | |
| 0 | 12 (16) |
| 1 | 39 (52) |
| 2 | 23 (30.7) |
| 3 | 1 (1.3) |
| Smoking status, n (%) | |
| Never smoked | 2 (2.7) |
| 0-20 pack-year history | 9 (12) |
| >20 pack-year history | 64 (85.3) |
| BMI | 26.3 (15-45) |
| CRP | 21.5 (1-267) |
| Albumin | 34 (20-46) |
| LDH | 302 (162-1334) |
| NLR | 5.4 (1.2-33.2) |
| Metastases at diagnosis, n (%) | |
| Brain | 24 (32) |
| Chest | 62 (82.7) |
| Other (including liver, adrenal etc.) | 55 (73.3) |
| No. of chemotherapy cycles completed | |
| 1 | 6 |
| 2 | 4 |
| 3 | 4 |
| 4 | 61 |
| Received radiotherapy, n (%) | 15 (20) |

BMI, body mass index; CRP, C-reactive protein; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; NLR, neutrophil-to-lymphocyte ratio.

### Survival Outcomes

**Association Between Clinical or Treatment Characteristics and PFS.** As found in Figure 1, the median PFS was 6.1 months. Table 2 illustrates the univariate analysis of PFS, wherein we identified statistically significant associations between improved PFS with higher albumin (HR = 0.94, 95% CI: 0.90–0.98, $p$ = 0.006), lower NLR (HR = 1.06, 95% CI: 1.02–1.11, $p$ = 0.004), lower LDH (HR = 1.001, 95% CI: 1.000–1.002, $p$ = 0.015), and total number of cycles of chemotherapy (HR = 0.60, 95% CI: 0.46–0.79, $p < 0.0001$). On multivariate analysis (Table 3), PFS was associated with older age (HR = 0.94, 95% CI: 0.90–0.98, $p$ = 0.006), lower NLR (HR = 1.08, 95% CI: 1.02–1.14, $p$ = 0.005), and total number of cycles of carboplatin and etoposide received (HR = 0.57, 95% CI: 0.37–0.89, $p$ = 0.011). Other parameters such as smoking history, BMI, and presence of brain or liver metastases were not found to be associated with PFS.

**Association Between Clinical or Treatment Characteristics and OS.** As found in Figure 2, the median OS was 9.2 months. In the univariate analysis revealed in Table 4, we found improved that OS was associated with higher albumin (HR = 0.95, 95% CI: 0.91–0.995, $p$ = 0.028), lower LDH (HR = 1.0, 95% CI: 1.0–1.0, $p$ = 0.006), and total number of cycles of carboplatin and etoposide received (HR = 0.37, 95% CI: 0.26–0.52, $p < 0.0001$). On multivariate analysis, a lower LDH (HR = 1.17, 95% CI: 1.02–1.33, $p = 0.024$) and total number of cycles of carboplatin and etoposide received (HR = 0.5, 95% CI: 0.30–0.84, $p$ = 0.008) were associated with improved OS (Table 5). We did not find any association with other tested parameters including age, sex, performance status, presence of metastases, CRP, and NLR with OS.

## Discussion

In the current era of immunotherapy, there are limited data on predictive and prognostic factors in the management of ES-SCLC. In an exploratory analysis of

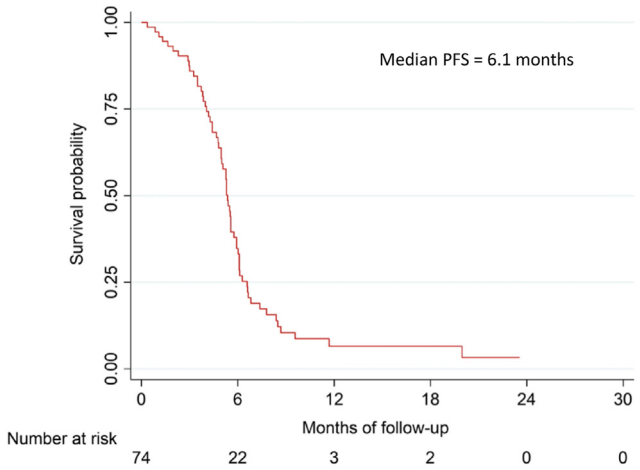


**Figure 1.** Kaplan-Meier curve illustrating PFS. PFS, progression-free survival.

atezolizumab maintenance therapy in the pivotal IMpower133 study, Eastern Cooperative Oncology Group performance status and liver metastases at baseline were identified as prognostic factors in reaching the maintenance phase.[8] Before immunotherapy, Ray et al.[9] revealed that the determinants of poor survival in ES-SCLC were a lack of complete response to chemotherapy (HR = 2.04), weight loss (HR = 1.76), high serum LDH (HR = 1.64), and high serum tumor proportion score level (HR = 2.47). Similarly, Tas et al.[10] found that response to chemotherapy was the key prognostic factor on the outcome of patients with ES-SCLC, whereas multiple metastases, weight loss, performance status, sex, serum LDH, and albumin were all predictive parameters of outcome in patients with ES-SCLC. In our study, we found that higher age, lower NLR, and total number of chemotherapy cycles were associated with improved PFS, whereas lower LDH and total number of cycles of chemotherapy received were associated with improved OS in our cohort of 75 patients. Our findings expand on these other studies that the clinical markers described are associated with an improved PFS and OS in patients with ES-SCLC treated with the current standard of care.

**Table 2.** Univariate Cox Regression Analysis for PFS

| Variable Name | Hazard Ratio | Confidence Interval | *p* Value |
|---|---|---|---|
| Age | 0.98 | 0.96-1.01 | 0.232 |
| Sex (female vs. male) | 0.88 | 0.49-1.38 | 0.455 |
| Smoking status | 1.39 | 0.74-2.58 | 0.293 |
| ECOG | 0.97 | 0.67-1.42 | 0.890 |
| BMI | 1.00 | 0.96-1.04 | 0.992 |
| Albumin | 0.94 | 0.90-0.98 | 0.006 |
| NLR | 1.06 | 1.02-1.11 | 0.004 |
| LDH | 1.001 | 1.000-1.002 | 0.015 |
| Cycles of EP | 0.60 | 0.46-0.79 | <0.0001 |

*Note:* Data cutoff: October 6, 2022.
BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; EP, etoposide platinum (carboplatin) chemotherapy; LDH, lactate dehydrogenase; NLR, neutrophil-to-lymphocyte ratio; PFS, progression-free survival.

**Table 3.** Multivariate Cox Regression Analysis for PFS

| Variable Name | Hazard Ratio | Confidence Interval | *p* Value |
|---|---|---|---|
| Age | 0.94 | 0.90-0.98 | 0.006 |
| Sex (female vs. male) | 1.20 | 0.62-2.33 | 0.588 |
| Albumin | 0.94 | 0.89-1.00 | 0.055 |
| NLR | 1.08 | 1.02-1.14 | 0.005 |
| LDH | 1.09 | 0.97-1.22 | 0.148 |
| Cycles of EP | 0.57 | 0.37-0.89 | 0.011 |

EP, etoposide platinum (carboplatin) chemotherapy; LDH, lactate dehydrogenase; NLR, neutrophil-to-lymphocyte ratio; PFS, progression-free survival.

Notably, the completion of all four cycles of chemotherapy was identified in our study to have a positive association with both improved OS and PFS. Cytotoxic chemotherapy has been found to modulate the antitumor immune response by promoting T-cell priming, tumor antigen release, and recruitment to the tumor which complements the effects of immune checkpoint blockade.[11] Nevertheless, as revealed in the CASPIAN 3-year survival update, at 36 months, there was a sustained OS benefit with durvalumab plus four cycles of platinum-etoposide versus six cycles of platinum-etoposide (HR = 0.71, 95% CI: 0.60–0.86; nominal $p$ = 0.0003), suggesting that more than four cycles of chemotherapy is not necessary for immune priming as it does not improve outcomes.[5]

Although higher serum albumin level correlated with improved PFS and OS in our univariate analysis, it did not maintain significance in the multivariate analysis. In a systematic review, higher pretreatment serum albumin was found to have prognostic significance in improving mortality for patients with a range of solid organ malignancies.[12] Malnutrition, proinflammatory cytokines, and systemic inflammatory response to tumor all result in lower serum albumin concentration.[13–16] Although serum albumin is not the only surrogate indicator for a patient's nutritional status, as a pretreatment prognostic factor, the test is relatively inexpensive, accessible, and reproducible. A decrease in serum albumin level has been found to be associated with increased morbidity and mortality which may be a reflection of its association with sarcopenia.[17]

Sarcopenia, a progressive skeletal muscle disorder, is quantified by low skeletal muscle density and higher fat mass on imaging and circulating biological markers.[18] Malignancy-associated cachexia is a syndrome resulting from abnormal metabolism, systemic inflammation,

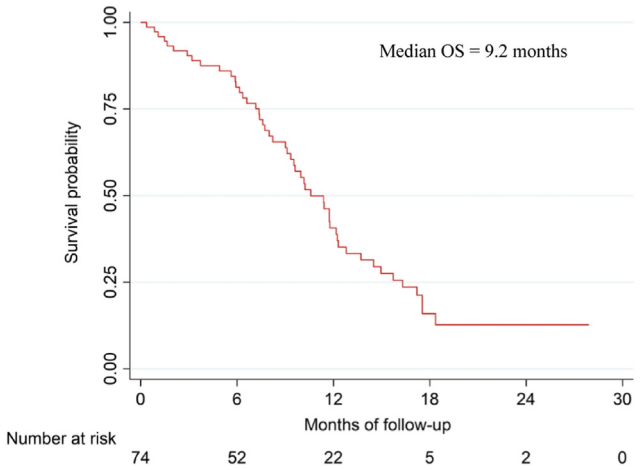


**Figure 2.** Kaplan-Meier curve illustrating OS. OS, overall survival.

reduced food intake, and sarcopenia.[19] Previous retrospective analyses have revealed a correlation between sarcopenia and poor survival in both gastrointestinal and ovarian malignancies and may be an emerging measure to assist in the prognostication of patients with ES-SCLC.[20–22]

High NLR defined as the absolute neutrophil and lymphocyte count has also been linked to poor survival; however, the prognostic value has not been found to be equal among all cancer subgroups.[23,24] In our study, we found that lower NLR was associated with an improvement in PFS. In a retrospective cohort study of 1714 patients treated with immune checkpoint inhibitors, Valero et al.[25] revealed that high NLR was associated with poorer OS and PFS; however, statistical significance was not observed in ES-SCLC.

High serum LDH level has been a well-recognized poor prognostic factor in patients with cancer, and elevated levels of LDH have been correlated with poor OS in ES-SCLC.[26,27] In a meta-analysis of 28 studies involving 4785 patients with SCLC, Zhang et al.[27] revealed that elevated LDH levels were associated with inferior OS (HR = 1.45, 95% CI: 1.27–1.66). Similarly, in our multivariate analysis, we found that lower LDH was associated with improved OS. LDH is a biomarker of cell turnover and has been traditionally used as a surrogate marker of tumor burden and sites of metastatic disease in patients with cancer.[28] Unlike the exploratory analysis of maintenance therapy by Reck et al.,[8] we did not find a correlation between sites of metastases, in particular the liver, and OS and postulate that this may be due to our smaller sample size.

**Table 4.** Univariate Cox Regression Analysis for OS

| Variable Name | Hazard Ratio | Confidence Interval | *p* Value |
|---|---|---|---|
| Age | 1.02 | 0.99-1.05 | 0.214 |
| Sex (female vs. male) | 1.59 | 0.89-2.82 | 0.109 |
| Albumin | 0.95 | 0.91-0.995 | 0.028 |
| NLR | 1.04 | 0.99-1.10 | 0.075 |
| LDH | 1.00 | 1.00-1.01 | 0.006 |
| Cycles of EP | 0.37 | 0.26-0.52 | <0.0001 |

EP, etoposide platinum (carboplatin) chemotherapy; LDH, lactate dehydrogenase; NLR, neutrophil-to-lymphocyte ratio; OS, overall survival.

**Table 5.** Multivariate Cox Regression Analysis for OS

| Variable Name | Hazard Ratio | Confidence Interval | *p* Value |
|---|---|---|---|
| Age | 1.01 | 0.96-1.07 | 0.644 |
| Sex (female vs. male) | 1.81 | 0.81-4.04 | 0.142 |
| Albumin | 0.98 | 0.91-1.05 | 0.558 |
| NLR | 1.04 | 0.98-1.10 | 0.177 |
| LDH | 1.17 | 1.02-1.33 | 0.024 |
| Cycles of EP | 0.50 | 0.30-0.84 | 0.008 |

EP, etoposide platinum (carboplatin) chemotherapy; LDH, lactate dehydrogenase; NLR, neutrophil-to-lymphocyte ratio; OS, overall survival.

In the era of precision oncology, molecular profiling is paramount to our understanding and management of ES-SCLC. Several groups have suggested that SCLC can be divided into four molecularly distinct subtypes on the basis of unique transcriptional factors and RNA sequencing profiles. These subtypes include SCLC-A defined by high expression of ASCL-1; SCLC-N, defined by high NeuroD1 expression; SCLC-Y, defined by high YAP1 transcriptional co-activator expression; and SCLC-P defined by POU2F3 domain expression.[25–27] A subsequent analysis by Gay et al.[29] suggested that the SCLC-Y subgroup should be redefined as SCLC-I (characterized by low expression of ASCL1, NeuroD1, and POU2F3) which exhibits an "inflamed" signature with a distinct T-cell inflamed phenotype.[29–31] Of these, the SCLC-I subtype was identified in a retrospective review of the IMpower133 study population to have a trend toward higher median OS with the use of atezolizumab compared with placebo (18 mo versus 10 mo) (HR = 0.566, 95% CI: 0.321–0.998).[29]

The limitations of our study include its retrospective nature and heterogeneity of data collection between institutions and potential variations in assessment of disease response. Other potential prognostic biomarkers such as tumor mutational burden or PD-L1 expression were not evaluated in this analysis; however, studies have suggested that neither biomarker seems to be predictive of outcomes.[6,7,32–34] Another limitation is that we did not define our cohort using molecular classifications however were limited by the scarcity of tumor tissue available owing to small diagnostic biopsies or limited cytologic aspirations, which is a widespread issue in this disease.[35]

In conclusions, this is the largest real-world study to our knowledge in patients with ES-SCLC treated with first-line chemoimmunotherapy that has studied the association between clinical characteristics and survival outcomes. In our study, we found that lower LDH was associated with improved OS, higher age and lower NLR were associated with improved PFS, and number of chemotherapy cycles received was associated with both an improved OS and PFS. These findings further emphasize the importance of the chemotherapy backbone in the treatment paradigm, most likely as a tumor antigen release catalyst to optimize the effect of the anti–PD-L1 agent. They also suggest that high baseline tumor burden and sarcopenia may play an important role in mitigating the effect of systemic therapy and warrant further study. Our understanding of clinical characteristics in a real-world scenario helps clinicians to better manage and educate patients with this aggressive lung cancer subtype. As the treatment landscape of ES-SCLC continues to evolve with the advent of immunotherapy, it will become imperative to provide the most optimal treatments which will predict the best outcomes, and therefore predictive and prognostic biomarkers, including clinical biomarkers, will be in high demand. Indeed, further studies are required to evaluate additional biomarkers and their association with outcomes in the pursuit of personalized therapies in this disease.

## CRediT Authorship Contribution Statement

**Surein Arulananda:** Conceptualization, Funding acquisition, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing—review and editing.

**Yang Wang:** Data curation, Investigation, Methodology, Roles/Writing—original draft, Writing—review and editing.

**Jared Mathai:** Data curation, Investigation, Methodology, Writing—review and editing.

**Paul Mitchell:** Resources, Supervision.

**Muhammad Alamgeer:** Writing—review and editing.

**Sagun Parakh:** Writing—review and editing.

**Eldho Paul:** Formal analysis, Writing—review and editing.

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